Methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate

To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-177 (1.1 g, 6.1 mmol), in anhydrous methylene chloride (10 mL) is added methanesulfonyl chloride (663  $\mu$ L, 8.6 mmol) at -30 °C, and the reaction is warmed to 0 °C. The reaction stirred 1 h, then filtered. The filtrate is added to N-methylbutylamine (2.1 mL, 18.3 mmol), and the reaction stirred at room temperature 16 h. The solution is concentrated under reduced pressure. Purification by flash chromatography affords the title compound in pure form. ESI MS m/z 250.2 [M + H]<sup>+</sup>.

### Step 2

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10

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamide dihydrochloride

2 HCI

3-{[butyl(methyl)amino]methyl}-5-methylbenzoate Methyl 20 (122)0.49 mmol) is dissolved in 2:1:1 mg, tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (41 mg, 1 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. redissolved The residue is in DMF (5 mL), and diisopropylethylamine (350 µL, 2 mmol), HATU (240 mg, 25 mmol), and  $(2R, 3S) - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[1 - (3 - 3)] - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - \{[$ ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride

prepared by the method in EXAMPLE SP-272 (215 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added.

10 The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 574.3 [M + H]<sup>+</sup>.

# EXAMPLE SP-189

 $3-\{[Butyl(methyl)amino]methyl\}-N-((1S,2R)-1-(3,5-$ 

difluorobenzy1)-2-hydroxy-3-{[3 (trifluoromethyl)benzyl]amino}propy1)-5-methylbenzamide
 dihydrochloride

2 HCl

20 Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (112 mg. mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (38 mg, 0.9 mmol), and the reaction stirred 16 h. The solution is 25 concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350  $\mu$ L, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5difluorophenyl)-1-{[1-(3ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride

prepared by the method in EXAMPLE SP-272 (201 mg, 0.44 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 592.3 [M + H]<sup>+</sup>.

#### EXAMPLE SP-190

 $3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1s,2R)-1-(3,5-1))$ 

difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2hydroxypropyl)benzamide dihydrochloride

Step 1

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Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate

To a solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.1 g, 16.8 mmol) in anhydrous methylene chloride (35 mL) at -30 °C is added methanesulfonyl chloride (1.82 mL, 23.5 mmol) followed by triethylamine (4.7 mL, 33.6 mmol). The reaction mixture is stirred for 45 min at 0 °C, and then filtered. The filtrate is added to N-methylbutylamine (6 mL, 50.4 mmol) and stirred at room temperature for 16 h. The solution is concentrated under reduced pressure, and the residue is purified by flash column chromatography (silica, 8% ethyl acetate/hexanes) to give the title compound. ESI MS m/z 314.1 30 [M + H]\*.

Step 2

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride

9 HCI

5 Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate (113 is mg, 0.36 mmol) dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (30 mg, 0.72 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced 10 pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (250  $\mu$ L, 1.44 mmol), HATU (170 mg, 0.45 mmol), and  $(2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - {[1 - (3 - amino - 4 - (3 - amino - 4$ ethynylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride prepared as in EXAMPLE SP-264 (170 mg, 0.4 15 mmol) are added. The reaction stirred at room temperature 16 Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as The residue is dissolved in diethyl ether (3 the free base. mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. 20 The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 638.2 [M + H]<sup>+</sup>.

### EXAMPLE SP-191

 $3-\{[Butyl(methyl)amino]methyl\}-N-((1S,2R)-1-(3,5-$ 

25 difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2hydroxypropyl)-5-methylbenzamide dihydrochloride

2 HCI

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (132 mg, mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (45 mg, 1.06 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350  $\mu$ L, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-amino-4-10 difluorophenyl)-1-{[1-(3-ethylphenyl)cyclopropyl]amino}butan-2-ol prepared by the method in EXAMPLE SP-272 (191 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium 15 sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. 20 The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 578.4 [M + H]<sup>+</sup>.

#### EXAMPLE SP-192

 $3-\{[Butyl(methyl)amino]methyl\}-N-\{(1S, 2R)-1-(3, 5-1)\}$ 

difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5methylbenzamide dihydrochloride

2 HCl

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (122 mg, mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (41 mg, 1.0 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (350  $\mu$ L, 2 mmol), HATU (240 mg, 0.63 mmol), and (2R,3S)-3-amino-4-(3,5-amino-4)10 difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (203 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, 15 brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 88 methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in 20 diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. m/z 552.3 [M + H]<sup>+</sup>.

# EXAMPLE SP-193

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

Analogous to the method described in EXAMPLE SP-184, 2 mL the stock solution is added to a solution of Nisoamylmethylamine (526 µL, 4.2 mmol) in anhydrous methylene chloride (1 mL), and the reaction mixture is stirred at room 5 temperature for 16 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with saturated sodium bicarbonate and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by 10 flash column chromatography (silica, 4% methanol/chloroform) provided the amine. The amine is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (42 mg, 1 mmol). The reaction is stirred 16 h and is concentrated under reduced pressure. The residue 15 is redissolved in DMF (5 mL), and diisopropylethylamine (355  $\mu$ L, 2 mmol), HATU (242 mg, 0.64 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-iodobenzyl)amino]butan-2-ol dihydrochloride (257 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. Purification by flash 20 column chromatography (silica, 7% methanol/chloroform) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS 25 m/z 664.2 [M + H]<sup>+</sup>.

#### EXAMPLE SP-194

 $3-\{[Butyl(methyl)amino]methyl\}-N-\{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1-$ 

phenylcyclopropyl)amino]propyl}-5-methylbenzamide
dihydrochloride

2 HCI

Analogous to the method in EXAMPLE SP-188, methyl 3-5 {[butyl(methyl)amino]methyl}-5-methylbenzoate (170 mg, 0.68 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (57 mg, 1.4 mmol), and the reaction stirred 2 h. The solution is concentrated under reduced pressure. The residue is redissolved in DMF (3 mL), and diisopropylethylamine (472  $\mu$ L, 10 2.7 mmol), HATU (322 mg, 0.85 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1-phenylcyclopropyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE S-XYZ (275 mg, 0.68 mmol) are added. The reaction stirred at room 15 temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 88 methanol/methylene chloride) 20 provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. m/z 550.3 [M + H]<sup>+</sup>.

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# EXAMPLE SP-195

3-{[Butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-methylbenzamide dihydrochloride

2 HCI

Analogous to the method in EXAMPLE SP-188, methyl 3-{[butyl(methyl)amino]methyl}-5-methylbenzoate (50 0.2 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (17 mg, 0.4 5 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced pressure. The is residue redissolved in DMF (2 mL), and diisopropylethylamine (140  $\mu$ L, 0.8 mmol), HATU (95 mg, 0.25 mmol), and (2R,3S)-3-amino-4-10 (3,5-difluorophenyl)-1-[(3-isopropylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-170, Step 4 (85 mg, 0.2 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, 15 brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 88 methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in 20 diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. m/z 566.3 [M + H]<sup>+</sup>.

#### EXAMPLE SP-196

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride Step 1

3-(Methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid

To a -70 °C stirred solution of oxazole (432 mg, 6.3 mmol) in tetrahydrofuran (10 mL) is added n-butyllithium (2.5 M in hexanes, 2.75 mL, 6.9 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 18.75 mL, 18.75 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of 3-iodo-5-(methoxycarbonyl)benzoic acid prepared by the method in EXAMPLE SP-281, step 1 (1.8 g, 6 mmol) in anhydrous tetrahydrofuran (10 mL) followed by palladium(0) tetrakis(triphenylphosphine) (291 mg, 0.25 mmol). The reaction mixture is heated at reflux for 15 h. reaction mixture is cooled, filtered through diatomaceous earth, diluted with ethyl acetate (50 mL), washed with water, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% methanol/methylene chloride) provides the title compound in pure form. ESI MS m/z 246.1 [M - H]-.

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Step 2

Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate

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To an ice-cold solution of 3-(methoxycarbonyl)-5-(1,3-oxazol-2-yl)benzoic acid (340 mg, 1.4 mmol) in anhydrous tetrahydrofuran (10 mL) is added lithium borohydride (250 mg,

slowly. The reaction is stirred 30 min, absolute ethanol (4 mL) is added, and the reaction is stirred The solution is poured onto ice containing excess 1 h. hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with water, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue is redissolved in 20% methanol/benzene (50 mL), and 2M trimethylsilyldiazomethane in hexane (0.9 mL, 1.8 mmol) The reaction is stirred 2 h at room temperature, is added. then concentrated under reduced pressure. The residue is redissolved in anhydrous methylene chloride (10 mL), cooled to -30 °C, then methanesulfonyl chloride (150  $\mu$ L, 1.9 mmol) and triethylamine (380 µL, 2.7 mmol) are added. The reaction is stirred at 0 °C 15 min, then N-methylbutylamine (480 µL, 4 mmol) is added, and the reaction is stirred 16 h at room temperature. The solution is concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 40-100% ethyl acetate/hexane gradient) provides the title compound in pure form. ESI MS m/z 303.3 [M + H]<sup>+</sup>.

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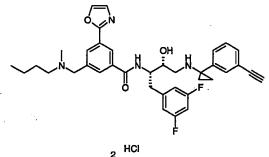
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# Step 3

3-{[Butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)benzamide dihydrochloride



Methyl 3-{[butyl(methyl)amino]methyl}-5-(1,3-oxazol-2-yl)benzoate (30 mg, 0.1 mmol) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide

monohydrate is added (10 mg, 0.2 mmol), and the reaction The solution is concentrated under reduced stirred 16 h. The residue is redissolved in DMF (1 mL), and pressure. diisopropylethylamine (70  $\mu$ L, 0.4 mmol), HATU (57 mg, 0.15  $(2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - {[1 - (3 - 3)]}$ mmol), and ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride The reaction stirred at room (203 mg, 0.5 mmol) are added. temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated 10 Purification by flash under reduced pressure. chromatography (silica, 9-10% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated 15 under reduced pressure to yield the title compound. m/z 627.3 [M + H]<sup>+</sup>.

#### EXAMPLE SP-197

3-{[Butyl(methyl)amino]methyl}-5-cyano-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide dihydrochloride

, HCI

3-Bromo-5-(methoxycarbonyl)benzoic acid (4 g, 15.4 mmol) (4.1)a, N-25 copper(I) cyanide 89.5 mmol) and methylpyrrolidinone (20 mL) is heated at 175 °C for 4 h. reaction is cooled, and water is added. The aqueous solution with 1N extracted with methylene chloride, washed sulfate), hydrochloric acid (aq), brine, dried (sodium

filtered, and concentrated under reduced pressure. The residue is dissolved in tetrahydrofuran (20 mL), cooled in an ice bath, and lithium borohydride (475 mg, 22 mmol) is added slowly. The reaction stirred at this temperature 2 h. Absolute ethanol (4 mL) is added dropwise, and the reaction stirred 30 min. The mixture is poured on ice containing excess hydrochloric acid. After gas evolution ceases, the solution is extracted with methylene chloride and concentrated under reduced pressure.

10 The residue is dissolved in 20% methanol/benzene (20 mL), and 2M trimethylsilyldiazomethane in hexane (1.3 mL, 2.6 mmol) is added. The reaction stirred at room temperature 2 h and is concentrated under reduced pressure. The residue is then dissolved in anhydrous methylene chloride (10 mL), cooled to -30 °C, then methanesulfonyl chloride (216  $\mu$ L, 2.8 mmol) and 15 triethylamine (556  $\mu$ L, 4 mmol) are added. The reaction is warmed to 0 °C and stirred 15 min, then filtered. The filtrate is added to N-methylbutylamine (5 mL) and stirred 16 h. The solution is concentrated under reduced pressure and 20 purification by flash chromatography (silica gel, 40% ethyl acetate/hexane) gives an oil. The oil (107 mg) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (35 mg, 0.8 mmol), and the reaction stirred 1.5 h. The solution is concentrated under 25 reduced pressure.

The residue is redissolved in DMF (3 mL), and diisopropylethylamine (280  $\mu$ L, 1.6 mmol), HATU (230 mg, 0.6 mmol),  $(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-{[1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3,5-difluorophenyl)-1-(3-mino-4-(3-mino$ and ethynylphenyl)cyclopropyl]amino}butan-2-ol dihydrochloride (206 mg, 0.5 mmol) are added. The reaction stirred at room temperature 16 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column

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chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 585.3 [M + H]<sup>+</sup>.

# EXAMPLE SP-198

 $N-\{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-$ 

10 hydroxypropy1}-3-{[(2-furylmethyl) (methyl) amino]methyl}-5methylbenzamide dihydrochloride

# Step 1

Methyl 3-bromo-5-(hydroxymethyl)benzoate

15 To an ice-cold, stirred solution of 3-bromo-5-(5.0 (methoxycarbonyl)benzoic acid 19.3 g, mmol) tetrahydrofuran (77.2 mL) is added borane dimethyl sulfide complex (10.6 mL, 2.0 M tetrahydrofuran, 21.1 mmol). reaction mixture is heated at 50 °C for 2 h. The reaction 20 mixture is quenched with methanol (50 mL) and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) affords the title compound.  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.03 (s, 1H), 7.90 (s, 1H), 7.69 (s, 1H), 4.69 (s, 1H), 3.91 (s, 3H), 2.83 (br s, 25 1H).

#### Step 2

Methyl 3-(hydroxymethyl)-5-methylbenzoate

a stirred solution of methyl 3-bromo-5-(hydroxymethyl)benzoate (4.53 g, 18.5 mmol) in dioxane (74 mL) is added cesium carbonate (6.0 g, 18.5 mmol), potassium 37 mmol), and palladium(0) (5.1)g, carbonate tetrakis(triphenylphosphine) (2.1 g, 1.85 mmol), followed by trimethyl boroxine (5.1 mL, 37 mmol). The reaction mixture is refluxed for 12 h, cooled to room temperature, and then partitioned between water and ethyl acetate. The organic layer is washed with water and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. 10 The black oil is adsorbed onto silica gel followed by purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) to provide the title compound. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta.7.75$  (s, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 5.31 (br s, 1H), 4.53 (s, 1H), 3.84 (s, 3H), 2.36 (s, 3H). 15

Step 3
Methyl

3-{[(2-furylmethyl)(methyl)amino]methyl}-5-

methylbenzoate

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solution of methyl 3 – ice-cold, stirred To 1.1 mmol) in (hydroxymethyl)-5-methylbenzoate (200 mg, methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and filtered. N-Methylfurfurylamine (367 mg, 3.3 mmol) is added to the filtrate and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), concentrated under reduced filtered, and Purification by flash column chromatography (silica, 50% ethyl

acetate/hexanes) provided the title compound.  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (d, J = 11 Hz, 2H), 3.79 (d, J = 6 Hz, 2H), 6.32 (d, J = 2 Hz, 1H), 6.21 (d, J = 3 Hz, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 3.53 (s, 2H), 2.39 (s, 3H), 2.23 (s, 3H).

5

Step 4

3-{[(2-Furylmethyl)(methyl)amino]methyl}-5-methylbenzoic acid

solution οf methyl 3-{[(2stirred а furylmethyl) (methyl) amino]methyl}-5-methylbenzoate (180 10 0.66 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (277 mg, 6.6 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate 15 concentrated under reduced pressure to provide the title compound. ESI MS m/z 258 [M + H]<sup>+</sup>.

Step 5

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

3-{[(2stirred solution of To a furylmethyl) (methyl) amino]methyl}-5-methylbenzoic 25 mg, 0.66 mmol) in methylene chloride (3 mL) is added HBTU (375 and N, Nmmol), 0.99 mmol), HOBt (134 mg,0.99 mg,

by

followed

diisopropylethylamine (0.334 mL, 1.98 mmol),

(2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3 - amino - 4 - (3 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (269 mg, 0.66 mmol), and the reaction mixture is 5 stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 10 methanol/chloroform) affords the title compound as the free The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane,

temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 576 [M + H]<sup>+</sup>.

20 mmol). The reaction mixture is stirred for 1 h at room

EXAMPLE SP-199

20 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

Step 1

30

Methyl 3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-

25 methylbenzoate

То an ice-cold stirred solution of methyl (hydroxymethyl) -5-methylbenzoate (200 mg, 1.1 mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 The reaction mixture is stirred for 15 min and filtered. 2-Methoxy-N-methyleneamine (0.354 mL, 3.3 mmol) is

added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provided the title compound.  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.75 (d, J = 5 Hz, 2H), 7.37 (s, 3H), 3.90 (s, 1H), 3.56 (s, 2H), 3.52 (t, J = 6 Hz, 2H), 3.34 (s, 3H), 2.61 (t, J = 6 Hz, 2H), 2.39 (s, 3H), 2.26 (s, 3H).

# Step 2

5

10

3-{[(2-Methoxyethyl) (methyl) amino] methyl}-5-methylbenzoic acid

15 To stirred solution of a methyl 3-{[(2methoxyethyl) (methyl) amino]methyl}-5-methylbenzoate 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol) and the reaction mixture stirred at room temperature for 2 h. 20 reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 238 [M + H]<sup>+</sup>.

#### 25 Step 3

N-{(1S, 2R)-1-(3, 5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

solution of · 3-{[(2-To а stirred methoxyethyl) (methyl) amino] methyl}-5-methylbenzoic mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318 5 0.84 mmol), HOBt (114 mg, 0.84 mmol), diisopropylethylamine (0.284 mL, 1.68 mmol), followed by (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(ethylbenzyl)amino]butan-2-ol prepared by the method in EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred 10 for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography pressure. (silica, 10% methanol/chloroform) affords the title compound 15 as the free base. The compound is dissolved in methanol (2 mL), and to this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol). The reaction mixture is stirred for 1 h The reaction mixture is then diluted at room temperature. with ethyl ether (10 mL). The precipitate that is formed is 20 collected by filtration to provide the title compound.

### EXAMPLE SP-200

m/z 554 [M + H]<sup>+</sup>.

 $3-\{[[2-(Diethylamino)ethyl](methyl)amino]methyl\}-N-\{(1S,2R)-1-(1$ 

25 (3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

hydroxypropyl}-5-methylbenzamide trihydrochloride

Step 1

Methyl 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoate

stirred solution То an ice-cold, of methyl 3-(hydroxymethyl)-5-methylbenzoate (200 mg, 1.19 mmol) and triethylamine (241 mg, 2.38 mmol) in methylene chloride (5 mL) is added methanesulfonyl chloride (191 mg, 1.67 mmol). reaction mixture is stirred for 15 min, the precipitate that formed is removed by filtration, and N, N-diethyl-N'methylethylenediamine (465 mg, 3.57 mmol) was added. The reaction mixture is stirred at room temperature for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gives the title compound.  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.02 (s, 2H), 7.33 (s, 1H), 3.56 (s, 3H), 3.48 (s, 2H), 2.95 (m, 4H), 2.75 (m, 4H), 2.41 (s, 3H), 2.31 (s, 3H), 1.21 (m, 6H).

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10

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Step 2

3-{[[2-(Diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid

20 Α mixture of methvl 3-{[[2-(diethylamino)ethyl] (methyl)amino]methyl}-5-methylbenzoate (296 mg, 1.01 mmol) and 3:1:1 methanol/tetrahydrofuran/2 N sodium hydroxide (10 mL) is stirred overnight and then partitioned between ethyl acetate and water. The aqueous 25 layer is acidified to pH 3 with 1 N hydrochloric acid and extracted with chloroform. The aqueous layer is concentrated under reduced pressure to give the title compound. <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$ , 7.99 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 4.56 (m, 2H), 4.31 (m, 2H), 3.98 (m, 2H), 3.17 (m, 4H), 2.51 (s, 3H), 2.50 (s, 3H), 1.27 (m, 6H). 30

# Step 3

 $3-\{[[2-(Diethylamino)ethyl](methyl)amino]methyl\}-N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2- \\$ 

5 hydroxypropyl}-5-methylbenzamide trihydrochloride

3 HCI

То a stirred solution of 3-{[[2-(diethylamino)ethyl](methyl)amino]methyl}-5-methylbenzoic acid (267 mg, 0.959 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of 10 EXAMPLE SP-272 (391 mg, 0.959 mmol), HOBt (129 mg, 0.959 mmol), and N, N-diisopropylethylamine (496 mg, 3.84 mmol) in methylene chloride (5 mL) is added EDC (331 mg, 1.73 mmol). The reaction mixture is stirred overnight and then partitioned between ethyl acetate and water. The organic layer is washed 15 with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9:1:1 methylene 20 chloride/methanol/ammonium hydroxide) gives the title compound. ESI MS m/z 595.4 [M + H]<sup>+</sup>.

# EXAMPLE SP-201

N-{(15,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-25 hydroxypropyl}-3-oxoindane-5-carboxamide

To 3-oxoindane-5-carboxylic acid (2.0 g, 11.5 mmol) in DMF (10 mL) is added disopropylethylamine (8 mL, 46 mmol), HATU (5.5 g, 14.4 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol

dihydrochloride prepared by the method of EXAMPLE SP-272 (5.6 g, 13.8 mmol). The reaction is stirred 1 h at room temperature. The reaction was partitioned between ethyl acetate and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) gives the title compound. ESI MS m/z 493.2 [M + H]<sup>+</sup>.

#### 15 EXAMPLE SP-202

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxyindane-5-carboxamide

To ice-cold solution of  $N-\{(1S, 2R)-1-(3, 5$ an 20 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3oxoindane-5-carboxamide prepared by the method in EXAMPLE SP-201 (66 mg, 0.13 mmol) in methanol (3 mL) is added sodium borohydride (20 mg, 0.52 mmol). The reaction stirred at room The reaction is concentrated under reduced temperature 3 h. 25 pressure, redissolved in water (3 mL) and partitioned into ethyl acetate. The organic layer is washed with water, saturated sodium bicarbonate, and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 495.2 [M + H]<sup>+</sup>.

30

EXAMPLE SP-203

 $N-\{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-3-\{[isobutyl(methyl)amino]methyl\}-5-methylbenzamide hydrochloride$ 

Step 1

5 Methyl 3-{[isobutyl(methyl)amino]methyl}-5-methylbenzoate

ice-cold. stirred solution of methyl 3--To an (hydroxymethyl)-5-methylbenzoate (200 1.1 mmol) in mg, methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 10 The reaction mixture is stirred for 15 min and N-Methylisobutylamine (287 mg, 3.3 mmol) is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, 15 and saturated sodium bicarbonate, dried (magnesium sulfate), concentrated under reduced pressure. filtered, and Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound. 1H NMR (300 MHz,  $CDCl_3$ )  $\delta$ .7.77 (s, 1H), 7.73 (s, 1H), 7.36 (s, 1H), 3.90 (s, 20 3H), 3.44 (s, 2H), 2.38 (s, 3H), 2.14 (s, 3H), 2.10 (d, J = 8Hz, 2H), 1.81 (m, 1H), 0.90 (d, J = 7 Hz, 6H).

Step 2

25 3-{[Isobutyl(methyl)amino]methyl}-5-methylbenzoic acid

To a stirred solution of methyl 3-{[isobutyl(methyl)amino]methyl}-5-methylbenzoate (120 mg, 0.48 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (200 mg, 4.8 mmol), and the

reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 236 [M + H]<sup>+</sup>.

# Step 3

5

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[isobutyl(methyl)amino]methyl}-5-

10 methylbenzamide hydrochloride

2 HCl

stirred solution of {[isobutyl(methyl)amino]methyl}-5-methylbenzoic acid (110 mg, 0.48 mmol) in methylene chloride (3 mL) is added HBTU (273 mg, 15 0.72 mmol), HOBt (97 mg, 0.72 mmol), diisopropylethylamine (0.243 mL, mmol), followed by 1.44 (2R, 3S) - 3 - amino - 4 - (3, 5 - diffuorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - [(3 - amino - 4ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (196 mg, 0.48 mmol), and the reaction mixture is 20 stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) affords a clear oil, which is dissolved 25 in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that

is formed is collected by filtration to provide the title compound. ESI MS m/z 552.5 [M + H]<sup>+</sup>.

# EXAMPLE SP-204

5 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-

[[methyl(pentyl)amino]methyl]benzamide dihydrochloride
Step 1

Methyl 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoate

10

To an ice-cold, stirred solution of methyl 3∸ (hydroxymethyl)-5-methylbenzoate (200 mg, 1.1 mmol) methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 The reaction mixture is stirred for 15 min and 15 mmol).  $N ext{-Methylpentylamine}$  (333 mg, 3.3 mmol) is added to filtered. the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), 20 filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 15% ethyl acetate/hexanes) provides the title compound.  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.75 (d, J = 4 Hz, 2H), 7.36 (s, 1H), 3.90 (s, 3H), 3.47 (s, 2H), 3.13 (t, J = 9 Hz, 3H), 2.39 (s, 2H), 2.34 (d, J25 = 8 Hz, 2H), 2.18 (s, 3H), 1.45 (m, 5H), 1.32 (m, 2H).

# Step 2

3-Methyl-5-{[methyl(pentyl)amino]methyl}benzoic acid

30

To a stirred solution of methyl 3-methyl-5- $\{[methyl(pentyl)amino]methyl\}$ benzoate (120 mg, 0.46 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (191 mg, 4.6 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 250 [M + H]<sup>+</sup>.

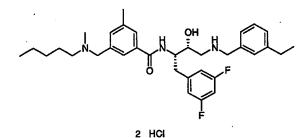
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5

# Step 3

 $N-\{(1S,2R)-1-(3,5-Difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1\}-3-methyl-5-$ 

{ [methyl (pentyl) amino] methyl} benzamide dihydrochloride



15

20

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of To a stirred solution 3-methyl-5-{[methyl(pentyl)amino]methyl}benzoic acid (110 mg, 0.44 mmol) in methylene chloride (3 mL) is added HBTU (250 mg, 0.66 mmol), HOBt (90 mg, 0.66 mmol), and N, N-diisopropylethylamine (0.222 mL, 1.32 mmol), followed by (2R,3S)-3-amino-4-(3,5difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (180 mg, 0.44 mmol), and the reaction mixture is stirred for 12 h at room temperature. reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric

acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 566.5 [M + H]<sup>+</sup>.

EXAMPLE SP-205

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N-{ $(1S,2R)-1-(3,5-Difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-3-{<math>[(2R)-2-(methoxymethyl)pyrrolidin-1-$ 

10 yl]methyl}-5-methylbenzamide dihydrochloride Step 1

Methyl 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate

15 То an ice-cold, stirred solution οf methyl 3-(hydroxymethyl)-5-methylbenzoate (200 1.1 mmol) in mg, methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 The reaction mixture is stirred for 15 min and mmol). (R)-2-(Methoxymethyl) pyrrolidine (380 mg, 3.3 mmol) 20 is added to the filtrate, and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. 25 Purification by flash column chromatography (silica, 50% ethyl acetate/hexanes) provides the title compound. 1H NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.11 (d, J =13 Hz, 1H), 3.90 (d, J = 6 Hz, 2H), 3.41 (m, 2H), 3.34 (m, 30 3H), 2.89 (m, 1H), 2.71 (m, 1H), 2.38 (s, 3H), 2.19 (m, 1H), 1.93 (m, 2H), 1.54 (m, 3H).

Step 2

3-{[(2R)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid

5 То stirred solution of methyl  $3-\{[(2R)-2-$ (methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate mg, 0.43 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (180 mg, 4.3 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, 10 dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound. ESI MS m/z 264 [M + H]<sup>+</sup>.

15 Step 3

N- $\{(1S, 2R)-1-(3, 5-Difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1\}-3-<math>\{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl\}-5-methylbenzamide dihydrochloride$ 

2 HCI

To a stirred solution of 3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid (113 mg, 0.43 mmol) in methylene chloride (3 mL) is added HBTU (165 mg, 0.66 mmol), HOBt (89 mg, 0.66 mmol), and N,N-disopropylethylamine (0.220 mL, 1.30 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE

SP-272 (175 mg, 0.43 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), 5 filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) affords a clear oil, which was dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is 10 then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 580.4 [M + H]<sup>+</sup>.

# 15 EXAMPLE SP-206

3-Bromo-5-{[butyl(methyl)amino]methyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide dihydrochloride

2 HCI

20 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (170 mg, 0.54) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4  $\mbox{mL})$ , and lithium hydroxide monohydrate is added (45 mg, 1.1 mmol), and the reaction stirred 16 h. The solution is 25 concentrated under reduced pressure. The residue is redissolved in DMF (5 mL), and diisopropylethylamine (375  $\mu$ L, 2.16 mmol), HATU (256 mg, 0.68 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (265

The reaction stirred at room 0.65 mmol) are added. The reaction mixture is diluted with temperature 1 h. methylene chloride, washed with water, and saturated sodium bicarbonate, dried (sodium sulfate), filtered, and Purification by flash concentrated under reduced pressure. column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (1 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. m/z 616.2 [M + H]<sup>+</sup>.

#### EXAMPLE SP-207

3-[(Butylamino)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-315 [(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide
dihydrochloride

Step 1

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10

Methyl 3-[(butylamino)methyl]-5-methylbenzoate

20 ice-cold, stirred solution οf methyl To mmol) (hydroxymethyl)-5-methylbenzoate (200 mq, 1.1 methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 The reaction mixture is stirred for 15 min and mmol). Butylamine (0.543 mL, 5.5 mmol) is added to the 25 filtered. and the reaction mixture is stirred at temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), 30 under filtered, and concentrated reduced pressure. Purification by flash column chromatography (silica, 89:10:1 chloroform/methanol/ammonium hydroxide) provides the title

compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.75 (s, 1H), 7.70 (s, 1H), 7.24 (br s, 1H), 4.42 (d, J = 9 Hz, 2H), 3.90 (s, 3H), 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, J = 7 Hz, 3H).

5

Step 2

Methyl 3-{[(tert-butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoate

To a stirred solution of methyl 3-[(butylamino)methyl]-5-10 methylbenzoate (70 mg, 0.30 mmol) in methylene chloride is triethylamine (0.046 mL, 0.33 mmol), and 4-added dimethylaminopyridine (4.0 mg, 0.03 mmol) followed by di-tertbutyl-dicarbonate (72 mg, 0.30 mmol). The reaction mixture is stirred at room temperature for 24 h, diluted with methylene 15 chloride, washed with 1 N hydrochloric acid, and brine. organic solution is dried (magnesium sulfate), filtered, and concentrated under reduced pressure to afford the title <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (s, 1H), 7.70 (s, compound. 1H), 7.24 (br s, 1H), 4.42 (d, J = 9 Hz, 2H), 3.90 (s, 3H), 20 3.16 (m, 2H), 2.38 (s, 3H), 1.64 (s, 2H), 1.44 (m, 9H), 1.27 (m, 2H), 0.89 (t, J = 7 Hz, 3H).

Step 3

25 3-{[(tert-Butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoic acid

To a stirred solution of methyl 3-{[(tert-butoxycarbonyl)(butyl)amino]methyl}-5-methylbenzoate (70 mg,

0.21 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (88 mg, 2.1 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate concentrated under reduced pressure to provide the title compound.

# Step 4

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3-[(Butylamino)methyl]-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methylbenzamide
dihydrochloride

2 HCI

stirred solution of 3-{[(tert-15 butoxycarbonyl) (butyl) amino] methyl}-5-methylbenzoic acid mg, 0.28 mmol) in methylene chloride (3 mL) is added HBTU (160 0.42 mg, mmol), HOBt (57 mg, 0.42 mmol), and N, Ndiisopropylethylamine (0.142 followed by mL, 0.84 mmol), (2R, 3S) - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)]]

20 ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (114 mg, 0.28 mmol), and the reaction mixture is stirred for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, saturated sodium bicarbonate, dried (magnesium sulfate), 25 filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL, 4 N dioxane, 20 mmol), and the reaction mixture is

stirred for 1 h at room temperature. The reaction mixture is then diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 538.5 [M + H]<sup>+</sup>.

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# EXAMPLE SP-208

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride

10 Step 1

Methyl 3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate

To an ice-cold, stirred solution of methyl 3--15 (hydroxymethyl)-5-methylbenzoate (200 1.1 mg, mmol) methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 mmol). The reaction mixture is stirred for 15 min and (S) - (+) -2 - (Methoxymethyl) pyrrolidine (380 mg, 3.3) filtered. 20 mmol) is added to the filtrate, and the reaction mixtire is stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced Purification by 25 pressure. flash column chromatography 15% acetate/hexanes) (silica, ethyl provides the title compound. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (s, 1H), 7.73 (s, 1H), 7.37 (s, 1H), 4.12 (d, J = 17 Hz, 1H), 3.90 (s, 3H), 3.85 (m, 2H), 3.51 (m, 2H), 3.44 (m, 2H), 3.15 (s, 1H), 2.38 (s, 3H), 1.94 (m, 3H), 1.72 (m, 3H). 30

Step 2

3-{[(2S)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid

solution of methyl  $3-\{[(2S)-2-$ To stirred (methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoate 5 mg, 0.50 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (211 mg, 5.0 mmol), and the reaction mixture stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and the filtrate 10 concentrated under reduced pressure to provide the title compound. ESI MS m/z 264 [M + H]<sup>+</sup>.

Step 3

15 N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamide dihydrochloride

2 HCI

To a stirred solution of 3-{[(2S)-2-20 (methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzoic acid (110 mg, 0.42 mmol) in methylene chloride (3 mL) is added HBTU (240 mg, 0.63 mmol), HOBt (85 mg, 0.63 mmol), and N,N-disopropylethylamine (0.212 mL, 1.26 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

25 ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (171 mg, 0.42 mmol). The reaction mixture is stirred

for 12 h at room temperature. The reaction mixture is diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash 10% methanol/chloroform) chromatography (silica, column affords a clear oil, which is dissolved in methanol (2 mL). To this solution is added hydrochloric acid (5 mL,4 N dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room The reaction mixture is then diluted with ethyl temperature. ether (10 mL). The precipitate that is formed was collected by filtration to provide the title compound. ESI MS m/z 580.4  $[M + H]^{+}$ .

### EXAMPLE SP-209

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}-3-{[(2-hydroxyethyl) (methyl)amino]methyl}-5methylbenzamide dihydrochloride

Step 1

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Methyl

3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-

20 methylbenzoate

To ice-cold stirred solution of methyl 3an (hydroxymethyl) -5-methylbenzoate (200 1.1 ma, mmol) in methylene chloride (2.2 mL) is added triethylamine (0.304 mL, 2.2 mmol) followed by methanesulfonyl chloride (0.116 mL, 1.5 The reaction mixture is stirred for 15 min and mmol). 2-Methoxy-N-methyleneamine (0.354 mL, 3.3 mmol) is added to the filtrate and stirred at room temperature for 5 h. The reaction mixture is diluted with methylene chloride (10 mL), washed with 1 N hydrochloric acid, and saturated sodium filtered, dried (magnesium sulfate), bicarbonate, Purification by flash concentrated under reduced pressure.

column chromatography (50% ethyl acetate/hexanes) provides the title compound. ESI MS m/z 238 [M + H]<sup>+</sup>.

Step 2

5 3-{[(2-Hydroxyethyl) (methyl)amino]methyl}-5-methylbenzoic acid

of solution methyl 3-{[(2-To а stirred hydroxyethyl) (methyl) amino] methyl}-5-methylbenzoate (180 0.72 mmol) in methanol (2 mL), tetrahydrofuran (1 mL), and water (1 mL) is added lithium hydroxide (302 mg, 7.2 mmol), 10 and the reaction mixture is stirred at room temperature for 2 h. The reaction mixture is concentrated under reduced pressure, dissolved in methylene chloride, filtered, and concentrated under reduced pressure to provide the title compound. ESI MS m/z 224 [M + H]<sup>+</sup>. 15

Step 3

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N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

To a stirred solution of 3-{[(2-hydroxyethyl)(methyl)amino]methyl}-5-methylbenzoic acid (140 mg, 0.56 mmol) in methylene chloride (3 mL) is added HBTU (318 mg, 0.84 mmol), HOBt (114 mg, 0.84 mmol), and N,N-disopropylethylamine (0.284 mL, 1.68 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol prepared by the method of EXAMPLE SP-272 (228 mg, 0.56 mmol). The reaction mixture is stirred for 24 h at room temperature, diluted with methylene chloride, washed with water, and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (10% methanol/chloroform) affords a clear oil, which is dissolved in methanol (2 mL). To this is added hydrochloric acid (5 mL of a 4 N solution in dioxane, 20 mmol), and the reaction mixture is stirred for 1 h at room temperature. The reaction mixture is diluted with ethyl ether (10 mL). The precipitate that is formed is collected by filtration to provide the title compound. ESI MS m/z 540.4 [M + H]<sup>+</sup>.

### 15 EXAMPLE SP-210

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3-Bromo-5-{[butyl(methyl)amino]methyl}-N-((1S, 2R)-1-(3, 5-difluorobenzyl)-2-hydroxy-3-{[3-

(trifluoromethyl)benzyl]amino}propyl)benzamide dihydrochloride

2 HCl

20 Methyl 3-bromo-5-{[butyl(methyl)amino]methyl}benzoate prepared by the method in EXAMPLE SP-190, Step 1 (200 mg, 0.64) is dissolved in 2:1:1 tetrahydrofuran/methanol/water (4 mL), and lithium hydroxide monohydrate is added (60 mg, 1.3 mmol), and the reaction stirred 16 h. The solution is reduced pressure. The concentrated under residue is 25 redissolved in DMF (5 mL), and diisopropylethylamine (445  $\mu$ L, 2.6 mmol), HATU (304 mg, 0.8 mmol), and (2R,3S)-3-amino-4- $(3, 5-difluorophenyl)-1-{[3-$ 

(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride

prepared by the method in EXAMPLE S-2511 (315 mg, 0.7 mmol) The reaction stirred at room temperature 16 h. are added. The reaction mixture is diluted with ethyl acetate, washed with water, and saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced 5 Purification by flash column pressure. chromatography (silica, 9% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced 10 pressure to yield the title compound. ESI MS m/z 656.2 [M + H]<sup>+</sup>.

# EXAMPLE SP-211

15 N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3{[isopentyl(methyl)amino]methyl}-5-methylbenzamide
dihydrochloride
Step 1

20 Methyl 3-{[isopentyl(methyl)amino]methyl}-5-methylbenzoate

To methyl 3-(hydroxymethyl)-5-methylbenzoate prepared by the method in EXAMPLE SP-198, Step 2 in anhydrous methylene chloride at -30 °C is added methanesulfonyl chloride (601 μL, 7.8 mmol), then triethylamine (1.5 mL, 11.1 mmol), and the reaction is stirred at 0 °C 15 min. The resulting precipitate is filtered, and the filtrate is added to N-methylisoamylamine (2.1 mL, 16.7 mmol). The reaction stirred at room temperature 16 h. The solution is concentrated under reduced pressure, redissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash

column chromatography (silica, 20% ethyl acetate/hexanes) provides the title compound. ESI MS m/z 264.2 [M + H]<sup>+</sup>.

Step 2

5 N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

3-{[isopentyl(methyl)amino]methyl}-5-10 To methyl 0.95 mmol) (250 methylbenzoate mg, tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (80 mg, 1.9 mmol), and the reaction is room temperature 16 h. The solution stirred at 15 concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (660  $\mu$ L, 3.8 mmol), HATU (540 mg, 1.4 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-ethynylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride (450 mg, 1.05 mmol) are added. The reaction The reaction mixture is stirred at room temperature 2 h. 20 diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene 25 chloride) provides the title compound as the free base. The dissolved in diethyl ether (3 mL) 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 588.3 [M + H]<sup>+</sup>.

EXAMPLE SP-212

N-((1S,2R)-1-(3,5-Difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3{[isopentyl(methyl)amino]methyl}-5-methylbenzamide dihydrochloride

2 HCI

To methyl 3-{[isopentyl(methyl)amino]methyl}-5methylbenzoate prepared by the method in EXAMPLE SP-211, Step 10 (160 mg, 0.61 mmol) in tetrahydrofuran/methanol/water (2:1:1, 8 mL) is added lithium hydroxide monohydrate (51 mg, 1.2 mmol), and the reaction is stirred at room temperature 16 The solution is concentrated under reduced pressure, redissolved in DMF (5 mL), and diisopropylethylamine (424  $\mu$ L, 2.4 mmol), HATU (290 mg, 0.8 mmol), and (2R,3S)-3-amino-4-15 (3,5-difluorophenyl)-1-{[1-(3-ethylphenyl)cyclopropyl]amino}-3-methylbutan-2-ol dihydrochloride prepared by the method in EXAMPLE SP-272 (291 mg, 0.7 mmol) are added. The reaction stirred at room temperature 2 h. The reaction mixture is diluted with ethyl acetate, washed with water, saturated 20 sodium bicarbonate, brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The 25 residue is dissolved in diethyl ether (3 mL) 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 592.3 [M + H]<sup>+</sup>.

EXAMPLE SP-213

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1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

5 Step 1: Methyl 1H-indole-5-carboxylate

To a mixture of indole-5-carboxylic acid (3.0 g) and triethylamine (1.9 g) in dry THF (100 mL) was added 1,1carbonyldiimidazole (3.08 g). The mixture was stirred for 30 minutes at room temperature, at which time methanol (25 mL) was added. The mixture was stirred at room temperature for 1 h, partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, anhydrous magnesium sulfate, dried over filtered concentrated under reduced pressure. Column chromatography on silica gel (200 mL) using CH2Cl2 as eluent to give 0.794 g of the title compound:  ${}^{1}H$  NMR (CDCl<sub>3</sub>)  $\delta$  3.93, 6.66, 7.28, 7.41, 7.91, 8.34, 8.42.

20 Step 2: Methyl 1-butyl-1H-indole-5-carboxylate

To a mixture of methyl 1H-indole-5-carboxylate (6.0 g) in methylsulfoxide (30 mL) was added potassium t-butoxide (3.88 g). The mixture was stirred at room temperature for 10 minutes at which time 1-iodobutane (1.8 mL) was added. The mixture was stirred at room temperature for 5 h then partitioned between water and methylene chloride. The layers

were separated and the organic layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 10% ethyl acetate in hexanes as eluent to give 6.18 g of the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.923, 1.38, 1.83, 3.9, 4.14, 6.58, 7.15, 7.34, 7.9, 8.39.

Step 3: 1-Butyl-1H-indole-6-carboxylic acid

To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.52 g) in methanol (25.0 mL) and water (5.0 mL) was added lithium hydroxide monohydrate (2.0 g). The mixture was heated to 60 °C for 6 h, cooled to room temperature, poured into 1N HCl (50mL) and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.496 g (72%) of the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.98 (t, J = 7.3 Hz, 3 H), 1.4 (m, 2 H), 1.9 (m, 2 H), 4.2 (m, 2 H), 6.57 (ss, J = 2.6 Hz, 1 H), 7.31 (ss, J = 3.1 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.89 (dd, J = 1.4, 8.4 Hz, 1 H), 8.24 (s, 1 H).

Step 4: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

To a mixture of 1-butyl-1H-indole-6-carboxylic acid (0.278 g) in methylene chloride (10 mL) was added triethylamine (0.129 g), HOBT (0.175 g) and, HATU (0.486 g).

The mixture was stirred at room temperature for 30 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.408 g) was added. The resulting mixture was stirred at room temperature for 18 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 3% methanol in methylene chloride as eluent to give 0.256 g of the title compound: MS (ESI+) for  $C_{32}H_{37}F_{2}N_{3}O_{2}$  m/z 542.2 (M+H).

EXAMPLE SP-201

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1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indoline-6-carboxamide hydrochloride

Step 1: Methyl 1-butylindoline-6-carboxylate

To a mixture of methyl 1-butyl-1H-indole-6-carboxylate,

(2.1 g) in glacial acetic acid (25 mL) was added sodium cyanoborohydride (2.28 g). The mixture was heated at 40 °C for 3 h then cooled to room temperature, partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 1.64 g of the title compound: ¹H NMR (CDCl<sub>3</sub>) δ 0.969, 1.43, 1.59, 2.99, 3.1, 3.4, 3.88, 7.07, 7.34.

Step 2: 1-Butylindoline-6-carboxylic acid

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To a mixture of Methyl 1-butylindoline-6-carboxylate (1.6 g) in methanol (20 mL) was added 1N NaOH (5.0 mL). The mixture was heated at 60 °C for 2 h then cooled to room temperature, poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 1.16 gof the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.974, 1.43, 1.60, 3.01, 3.11, 3.42, 7.1, 7.43.

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Step 3: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indoline-6-carboxamide hydrochloride

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To a mixture of 1-butylindoline-6-carboxylic acid (0.2 g) in methylene chloride was added triethylamine (0.0.27 g), HOBT (0.125 g) and, HATU (0.347 g). The mixture was stirred at 40 °C for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.346 g) was added. The resulting mixture was stirred at 40 °C for 5 h then partitioned between water and methylene chloride. The layers were separated and the organic layer washed with water followed by brine and dried over anhydrous magnesium sulfate. Column chromatography on silica gel (100 mL) using 5% methanol

in methylene chloride as eluent to give 0.100 g of the title compound: MS (ESI+) for  $C_{32}H_{39}F_2N_3O_2$  m/z 535.9 (M+H)<sup>+</sup>.

# EXAMPLE SP-215

1-Butyl-N-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-6-carboxamide

Step 1: 3-[(E)-(Tert-butylthio)diazenyl]-4-methylbenzoic acid

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To a mixture of 3-amino-4-methyl benzoic acid (5.0 g) in water (50 mL) was added concentrated hydrochloric acid (15 mL). The mixture was chilled to 0 °C in an ice/acetone bath. Sodium nitrite (2.28 g) was dissolved in water (10 mL) and 15 slowly added to the mixture at 0 °C. The pH was adjusted to 6 with saturated sodium acetate and 2-methyl-2-propanethiol (1.8 mL) was added. The mixture was stirred for 1 h and the resulting solids were collected by filtration, washed with water and dried under reduced pressure to give 5.7 g of the title compound:  ${}^{1}H$  NMR (CDCl<sub>3</sub>)  $\delta$  1.61, 2.20, 7.38, 7.55, 9.67.

Step 2: 1H-Indazole-6-carboxylic acid

25 3-[(E)-(tert-butylthio)diazenyl]-4-To of mixture (5.7 methylbenzoic acid g) in nitrogen degassed methylsulfoxide (90 mL) was added potassium t-butoxide (25.0 The mixture was stirred at room temperature for 24 h then poured onto ice and acidified to pH 4 with concentrated hydrochloric acid. 30 The mixture was extracted with diethyl

ether and the organic layer washed with brine. The organic layer was dried over anhydrous magnesium sulfate and decolorizing carbon then concentrated under reduced pressure to give 1.2 gof the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.963, 1.36, 1.95, 4.48, 7.81, 7.88, 8.08, 8.29.

Step 3: Methyl 1H-indazole-6-carboxylate

To a mixture of 1H-indazole-6-carboxylic acid (1.0 g) in methylene chloride (15 mL) was added EDC (1.8 g), HOBT (1.27 10 g), and triethylamine (1.29 mL). The mixture was heated to 40 °C for 30 minutes at which time methanol (10.0 mL) was added. The mixture was stirred at 40 °C for 18 h. The mixture was removed from heat, cooled to room temperature and poured into methylene chloride. The mixture was washed twice with water 15 brine, dried over anhydrous sodium sulfate concentrated under reduced pressure to give 0.955 g of the title compound:  ${}^{1}H$  NMR (CDCl<sub>3</sub>)  $\delta$  3.98, 7.81, 7.86, 8.16, 8.29, 10.6.

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Step 4: Methyl 1-butyl-1H-indazole-6-carboxylate

To a mixture of methyl 1H-indazole-6-carboxylate (0.95 g) in DMF (10 mL) was added 60% NaH (0.216 g). The mixture was heated to 60 °C and 1-iodobutane (0.61 mL) was added. The mixture was heated at 60 °C for 72 h and 1-iodobutane (0.61 mL) was added every 24 h. The mixture was removed from heat and cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic

layer washed three times with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.356 g of the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.938, 1.34, 1.92, 3.97, 4.43, 7.73, 7.79, 8.03, 8.18.

Step 5: 1-Butyl-1H-indazole-6-carboxylic acid

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To a mixture of methyl 1-butyl-1H-indazole-6-carboxylate  $(0.356~\mathrm{g})$  in methanol  $(10~\mathrm{mL})$  was added saturated sodium bicarbonate  $(5~\mathrm{mL})$ . The mixture was heated at  $60~\mathrm{^{\circ}C}$  for 2 h at which time 1N NaOH  $(5~\mathrm{mL})$  was added and the mixture heated to  $80~\mathrm{^{\circ}C}$  for 18 h. The mixture was cooled to room temperature, poured into 1N HCl  $(50~\mathrm{mL})$ , and extracted with ethyl acetate. The ethyl acetate extract dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 0.310 g of the title compound:  $^{1}$ H NMR  $(CDCl_{3})$   $\delta$  0.964, 1.96, 4.48, 7.81, 7.89, 8.29, 8.46.

Step 6: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-6-carboxamide

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To a mixture of 1-butyl-1H-indazole-6-carboxylic acid (0.2 g) in methylene chloride (20 mL) was added triethylamine (0.182 g), HOBT (126 g), and HATU (0.348 g). The mixture was

stirred at 40 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.35 g) was added. The mixture was stirred at 40 °C for 3 h then poured into methylene chloride (50 mL), washed with water then brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent

to give 0.2 g of the title compound: MS (ESI+) for C31H36F2N4O2

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EXAMPLE SP-216

m/z 534.9 (M+H)<sup>+</sup>.

1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

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Step 1: Methyl 4-methyl-3,5-dinitrobenzoate

To a mixture of 3,5 dinitrotoluic acid (16 g) in methanol (10 mL) was added sulfuric acid (15 mL). The mixture was 20 heated to 75 °C for 72 h, removed from heat and cooled to room temperature. The solvents were removed under pressure and the residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with 2 N NaOH followed by water. The organic layer was dried over 25 anhydrous magnesium sulfate, filtered and concentrated to give 16.28 g (96%) of the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.65 (s, 3 H), 4.02 (s, 3 H), 8.61 (s, 2 H

Step 2: Methyl 4-[(E)-2-(dimethylamino)ethenyl]-3,5-30 dinitrobenzoate

To a mixture of methyl 4-methyl-3,5-dinitrobenzoate (5.6 g) in toluene (20 mL) was added dimethylformamide dimethyl acetal (4.17 g) and 5-sulfo salycylic acid hydrate (0.1 g). The mixture was heated to 110 °C for 19 h, removed from heat and cooled to room temperature. The solvents were removed under reduced pressure at which time hexanes was added to the residue and the residue was filtered to give 6.85 g of the title compound:  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  2.97, 3.96, 5.54, 6.74, 8.33.

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Step3: Methyl 4-amino-1H-indole-6-carboxylate

To a mixture of methyl  $4-[(E)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (19.3 g) in ethyl acetate (200 mL) was added 5% palladium on carbon (1.5 g). The mixture was placed under 45 PSI H<sub>2</sub> and shaken overnight. The mixture was filtered through celite and concentrated. The residue was dissolved in <math>CH_2Cl_2$  to which was added ((1:1) H<sub>2</sub>O:conc. HCl (250 mL)). The resulting solids were collected by filtration, dissolved in ethyl acetate and washed with 2N NaOH. The ethyl acetate layer with anhydrous magnesium sulfate, filtered and concentrated to give 7.4 g if the title compound:  $^1H$  NMR (CDCl<sub>3</sub>)  $\delta$  3.91, 4.01, 6.51, 7.09, 7.27, 8.40.

25 Step 4: Methyl 4-[(methylsulfonyl)amino]-1H-indole-6-carboxylate

To a mixture of methyl 4-amino-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added 4-dimethylaminopyridine (1.46 g) and methanesulfonyl chloride (0.6 g). The mixture was heated to 60 °C for 3 h, cooled to room temperature, and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed three times with brine, dried over anhydrous sodium sulfate and concentrated to give 0.71 g of the title compound:  $^1$ H NMR (CDCl<sub>3</sub>)  $\delta$  3.02, 3.94, 6.69, 7.42, 7.81, 8.04.

Step 5: Methyl 4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylate

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15 То a mixture of Methyl 4-[(methylsulfonyl)amino]-1Hindole-6-carboxylate (0.6 g) in THF (10 mL) was potassium carbonate (0.309 g) and iodomethane (0.63 mL). mixture was stirred at room temperature for 4 h then heated to 40 °C overnight. Iodomethane (0.3 mL) was added and the 20 mixture heated an additional 3 h. The mixture was cooled to room temperature, partitioned between water and diethyl ether, dried over anhydrous sodium sulfate and concentrated. residue was dissolved in ether and decolorizing carbon (2 g) was added and the mixture refluxed for 5 minutes then filtered 25 through celite while hot. The ether was removed under reduced

pressure to give 0.437 g of the title compound: MS (ESI+) for C12 H14 N2 O4 S1 m/z 321.1 (M+K).

Step 6: 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-5 carboxylic acid

To a mixture of methyl 4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylate (0.437 g) in DMF(15 mL) was added potassium hydroxide (0.087 g) and iodobutane (0.34 mL). mixture was heated to 70 °C for 6 h. then stirred at room temperature for 72 h. The mixture was partitioned between water and ethyl acetate, the layers were separated and the organic layer washed three times with water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in methanol (5 mL) to which was added 1N NaOH (2 mL) and the mixture heated to 50 °C for 1 h. The mixture was cooled to room temperature and poured into water and washed with ether. The aqueous layer was acidified to pH 4 with 1N HCl and the product extracted into ethyl acetate which was dried over anhydrous sodium sulfate, filtered and concentrated to dryness to give 0.377 g of the title compound:  ${}^{1}H$  NMR (CDCl<sub>3</sub>)  $\delta$  0.973, 1.38, 1.87, 3.01, 3.45, 4.21, 6.71, 7.36, 7.82, 8.18.

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25 Step 7: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4[methyl(methylsulfonyl)amino]-1H-indole-6-carboxamide

To a mixture of 1-Butyl-4-[methyl(methylsulfonyl)amino]-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (15 mL) was added triethylamine (0.156 g), HOBT (0.105 g), and HATU (0.293 g). The mixture was stirred at 39 °C for 10 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.293 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water followed by brine then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent to give 0.21 g of the title compound: MS (ESI+) for C34H42F2N4O4S1 m/z 640.8 (M+H).

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# EXAMPLE SP-217

N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)isonicotinamide hydrochloride

# 20 Step 1: 2-Chloroisonicotinonitrile

4-cyanopyridine-N-oxide (10.0 g) was added to phosphorus oxychloride (85 mL) and heated to 110 °C for 2.5 h. The mixture was cooled to room temperature and the excess phosphorus oxychloride removed under reduced pressure. The residue dissolved in water and basic with was extracted into concentrated ammonia. The product was

methylene chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using methylene chloride as eluent to give 7.19 g of the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  7.48, 7.6, 8.6.

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Step 2: 2-(Dipropylamino)isonicotinonitrile

2-Chloroisonicotinonitrile (1.0 g) and dipropylamine (10 mL) were placed in a sealed heavy wall tube and heated to 100 °C for 18 h. The mixture was removed from heat and cooled to room temperature. The dipropylamine was removed under reduced pressure and the residue chromatographed on silica gel using 2% ethyl acetate in hexanes as eluent to give 1.06 g of the title compound: MS (ESI+) for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub> m/z 204.1 (M+H)<sup>+</sup>.

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Step 3: 2-(Dipropylamino)isonicotinic acid hydrochloride

2-(Dipropylamino)isonicotinonitrile (1.0 g) was dissolved in concentrated hydrochloric acid (30 mL) and heated at 65 °C for 3 h. The solvents were removed under reduced pressure to give 1.27 g of the title compound: MS (ESI+) for  $C_{13}H_{20}N_2O_2$  m/z 237.3 (M+H)<sup>+</sup>.

Step 4: N-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-

25 ethylbenzyl)amino]-2-hydroxypropyl}-2 (dipropylamino)isonicotinamide hydrochloride

mixture of 2-(Dipropylamino) isonicotinic To hydrochloride (0.2g) in methylene chloride (15 mL) was added triethylamine (0.195 g), HOBT (0.105 g), and HATU (0.293 g). The mixture was stirred at 39 °C for 10 minutes at which time 5 (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - [(3 - amino - 4 - (ethylbenzyl)amino]butan-2-ol (0.285 g) was added. The mixture was stirred at 40 °C for 4 h then poured into methylene chloride (50 mL), washed with water then brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. 10 Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride as eluent and conversion to the hydrochloride salt gave 0.105 g of the title compound: MS (ESI+) for  $C_{31}H_{40}F_2N_4O_2$  m/z 539.3 (M+H)<sup>+</sup>.

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EXAMPLE SP-218

1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide

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Step 1: Methyl 4-iodo-1H-indole-6-carboxylate

To a mixture of methyl 4-amino-1H-indole-6-carboxylate (EXAMPLE SP-216, step 3) (3.2 g) in water (50 mL) was added concentrated hydrochloric acid (5 mL). The mixture was chilled to below 5 °C with the addition of ice. To this was added sodium nitrite (1.16 g) dissolved in water (10 mL). The

mixture was stirred chilled for 1 h followed by addition of sodium iodide (3 g) in water (20 mL). The mixture was stirred for 30 minutes, filtered and the solids collected by filtration were washed with water and dried at 50 °C. The solids turned black and gas evolved rapidly upon drying. Column chromatography on silica gel (200 mL) using 20 % hexanes in CH2Cl2 as eluent to give 0.82 g of the title compound:  ${}^{1}H$  NMR (CDCl<sub>3</sub>)  $\delta$  3.94, 6.55, 7.43, 8.14, 8.22, 8.62.

10 Step 2: Methyl 1-butyl-4-iodo-1H-indole-6-carboxylate

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To a mixture of methyl 4-iodo-1H-indole-6-carboxylate (1.0 g) in DMF (10 mL) was added potassium hydroxide (0.392 g) and 1-iodobutane (0.8 mL). The mixture was heated to 80 °C for The mixture was cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed twice with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 20 mL) using 20% ethyl acetate in hexanes as eluent to give 0.73 g of the title compound:  $^{1}$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.940, 1.32, 1.81, 3.95, 4.15, 6.45, 7.31, 8.09, 8.18.

1-Butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic Step 3: 25 acid

To a -72 °C solution of oxazole (0.069 g) in dry THF (20 mL) was added dropwise 1.6 M N-butyl lithium (0.68 mL). mixture was stirred at -72 °C for 30 minutes at which time 1.0 M zinc chloride (3.3 mL) was added. The mixture was allowed to warm to 0 °C at which time methyl 1-butyl-4-iodo-1H-indoletetrakis triphenylphosphine (0.37)g) and 6-carboxylate palladium (0) (0.07 g) were added and the mixture heated to 85 The mixture was heated at 85 °C for 20 h then cooled to room temperature and partitioned between water and ethyl acetate. The layers were separated and the organic layer washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography was performed on silica gel (100 mL) using 20% ethyl'acetate in hexanes as eluent. The residue was dissolved in methanol (10 mL) and 1N NaOH (3 mL) and heated at 60 °C for 2 h. mixture was acidified to pH 4 with 1N HCl and extracted with The ethyl acetate extracts were dried over ethyl acetate. anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.2 g of the title compound: MS (ESI+) for  $C_{16}H_{16}N_2O_3$  m/z 283.16 (M+H)<sup>+</sup>.

Step 4: 1-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide

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To a mixture of 1-butyl-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxylic acid (0.2g) in methylene chloride (20 mL) was added 1,1-carbonyldiimidazole (0.114 g). The mixture was stirred at room temperature for 1 h at which time (2R,3S)-3-amino-4-(3,5-

difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.265 g) dissolved in methylene chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 65% methylene chloride, 30 % hexanes, and 5% methanol as eluent to give 0.0985 g of the title compound: MS (ESI+) for  $C_{35}H_{38}F_2N_4O_3$  m/z 601.99 (M+H) $^+$ .

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### EXAMPLE SP-219

1-Butyl-4-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

15 Step 1: Methyl 1-butyl-4-cyano-1H-indole-6-carboxylate

То mixture methyl 1-butyl-4-iodo-1H-indole-6of carboxylate (EXAMPLE SP-218, Step 4) (1.47 g) in N-methyl pyrrolidinone (15 mL) was added copper (I) cyanide (1.1 g). 20 The mixture was heated to 150 °C for 6 h, removed from heat and cooled to room temperature. The mixture was partitioned between water and ethyl acetate and the layers were separated. The organic layer was washed three times with water, dried over anhydrous sodium sulfate and concentrated under reduced 25 pressure. Column chromatography on silica gel (100 mL) using 20% ethyl acetate as eluent to give 0.5 g of the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.955, 1.32, 1.85, 3.98, 4.23, 6.76, 7.43, 8.16, 8.30.

30 Step 2: 1-Butyl-4-cyano-1H-indole-6-carboxylic acid

To a mixture of methyl 1-butyl-4-cyano-1H-indole-6-carboxylate (10.5 g) in methanol (15 mL) was added 1N NaOH (3.0 mL). The mixture was heated at 40 °C for 2 h then cooled to room temperature. The mixture was poured into 1N HCl and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous magnesium sulfate and concentrated to give 0.45 g of the title compound:  $^1$ H NMR (CDCl<sub>3</sub>)  $\delta$  0.973, 1.38, 1.88, 4.27, 6.79, 7.48, 8.24, 8.38.

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Step 3: 1-Butyl-4-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

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To a mixture of 1-butyl-4-cyano-1H-indole-6-carboxylic acid (0.29 g) in methylene chloride (10 mL) was added 1,1-carbonyldiimidazole (0.194 g) and triethylamine (0.267 g). The mixture was stirred at room temperature for 45 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.5 g) dissolved in methylene chloride (10 mL) was added. The mixture was stirred at room temperature for 18 h then poured into methylene chloride (50 mL), washed with water followed by brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in

methylene chloride as eluent to give 0.47 g of the title compound: MS (ESI+) for  $C_{33}H_{36}F_2N_4O_2$  m/z 559.0  $(M+H)^+$ .

EXAMPLE SP-220

5 4-Butyl-N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

Step 1: Methyl 4-hydroxy-3-iodo-5-nitrobenzoate

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To a solution of methyl 4-hydroxy-3-nitrobenzoate (2.0 g) in acetic acid (15 mL) was added iodine monochloride (1.65 mg) in acetic acid, and the mixture was stirred at 100 °C for 1.5 h. After cooling to room temperature, the mixture was poured into water (200mL), and stirred for 30 min. The mixture was filtered and washed with water and hexanes. The yellow powder was collected by filtration and dried in vacuum oven overnight to give 2.99 g of the title compound: ¹H NMR (300 MHz, CDCl<sub>3</sub>) 5.11.68, 8.81, 8.72, 3.96.

Step 2: Methyl 3-amino-4-hydroxy-5-iodobenzoate

To a mixture of methyl 4-hydroxy-3-iodo-5-nitrobenzoate (2.99 g) in ethanol (40 mL) was added tin (II) chloride (10 g) portion wise. After stirring for 1 h at reflux, the mixture was cooled to 0 °C and quenched by saturated potassium carbonate (100 mL). The mixture was filtered through

diatomaceous earth and the filtrate was extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2.5 g of the title compound:  $^{1}$ H NMR (300 MHz, DMSO- $d_{6}$ )  $\delta$ .7.50, 7.24, 3.75.

Step 3: Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

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To an ice-cold, stirred solution of Methyl 3-amino-4-hydroxy-5-iodobenzoate (2.3 g) and sodium bicarbonate (1.5 g) in 1:1 isobutyl methyl ketone/water (80 mL) was added chloroacetyl chloride (1.1 g), and the reaction mixture was stirred for 1 h. The mixture was warmed to room temperature and heated at reflux for 18 h. After overnight, a beige solid formed. The mixture was filtered, and washed with water and hexanes to give 2.4 g of the title compound:  $^1$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$ .10.98, 7.89, 7.47, 4.79, 3.82.

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Step 4: Methyl 4-butyl-8-iodo-3-oxo-3;4-dihydro-2H-1,4-benzoxazine-6-carboxylate

To a solution of Methyl 8-iodo-3-oxo-3,4-dihydro-2H-1,4-25 benzoxazine-6-carboxylate (2.64 g) and potassium carbonate (5 g) in DMSO (20 mL) was added bromobutane (5 g), and the reaction mixture was stirred for 1 h at 80 °C. The mixture was cooled to room temperature, diluted with 1:1 ethyl

acetate/hexanes (100 mL) and water (160 mL), and separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:10 ethyl acetate/hexanes) afforded 2.24 g of the title compound:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .8.13, 7.63, 4.74, 3.96, 3.92, 1.64, 1.42, 0.97.

Step 5: Methyl 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-10 6-carboxylate

A solution of Methyl 4-butyl-8-iodo-3-oxo-3,4-dihydro-2H1,4-benzoxazine-6-carboxylate (680 mg) and 9-BBN (900 mg) in

15 tetrahydrofuran (30 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.22 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% ethyl acetate/hexanes) afforded 600 mg of the title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ.7.75, 7.28, 4.34, 3.86, 3.36, 3.28, 1.58, 1.40, 0.96.

25 Step 6: Methyl 4-butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

-70 °C solution of oxazole (227 mg) in tetrahydrofuran (10 mL) was added n-butyllithium (2.5 M in hexanes, 2 mL). After stirred at -70 °C for 30 min, zinc chloride (1 M in ethyl ether, 13 mL) was added: The mixture was warmed to 0 °C for 1 h. To this mixture was then added 4-butyl-8-iodo-3,4-dihydro-2H-1,4-benzoxazine-6carboxylate (600 mg, 1.6 mmol) in THF (5 mL) followed by tetrakis triphenylphosphine palladium (0) (115 mg). mixture was heated at reflux for 3 h, diluted with ethyl acetate (300 mL) and washed with water followed by brine. The organic solution was dried (sodium sulfate) and concentrated under reduced pressure. Purification by silica gel plug (1:1 acetate/hexanes) provided 363 mg of the title compound: 1H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.96, 7.73, 7.40, 7.28, 4.44, 3.90, 3.43, 3.34, 1.61, 1.41, 0.98.

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Step 7: 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid

20 To a stirred solution of Methyl 4-butyl-8-(1,3-oxazol-2yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (474 mg) methanol (20 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The residue was diluted with water and washed with 25 ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4  $\times$  100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 450 mg of the title compound: 30  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)

δ<sub>.</sub>11.60, 8.08, 7.74, 7.46, 7.37, 4.46, 3.43, 3.34, 1.62, 1.41, 0.98.

Step 8: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

A solution of 4-Butyl-8-(1,3-oxazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid (450 mg, HBTU (853 mg), and diisopropylethylamine (580 mg) was stirred in methylene chloride (15 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol mg) in methylene chloride (7 mL) was added and the reaction mixture was stirred overnight. The mixture was filtered with methylene chloride, dried (magnesium sulfate), 15 concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 400 mg of the title compound: ESI MS m/z 619 [M + H]+.

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# EXAMPLE SP-221

4-Butyl-8-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

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Step 1: Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate

To a stirred solution of  $Pd(OAc)_2$  (144 mg), BINAP (1.2 g), and cesium carbonate (8.4 g) in toluene (100 mL) was added butylamine (1.6 mL), and the mixture was heated at 80 °C for 15 min. A solution methyl 3,5-dibromo-4-methoxybenzoate (4.2 g) in toluene (30 mL) was added dropwise over 20 min. The mixture was refluxed overnight. The mixture was cooled to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 3.5 g of the title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta.7.52$ , 7.19, 3.90, 3.88, 3.18, 1.66, 1.46, 0.97.

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Step 2: Methyl 3-bromo-5-(butylamino)-4-hydroxybenzoate

15 To a -78 °C solution of the Methyl 3-bromo-5-(butylamino)-4-methoxybenzoate (520 mg) in methylene chloride (10 mL) was added BBr<sub>3</sub> (8 ml of 1.0 M solution in methylene chloride) dropwise and the reaction mixture was stirred for 18 h. The mixture was concentrated under reduced pressure, and the 20 residue was dissolved in methylene chloride and saturated sodium bicarbonate was added. The mixture was cooled to 0  $^{\circ}\text{C}$ and methanol was added dropwise. After stirring for 30 min, the mixture was stirred at room temperature for 1 h. The solvent was removed, and the residue dissolved in methylene chloride, washed with water, saturated sodium bicarbonate (15 25 mL), and brine, dried (magnesium sulfate), filtered, concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:20, ethyl acetate/hexanes) provided 440 mg of the title compound: 1H NMR (300 MHz, CDC13) 30  $\delta.7.52$ , 7.19, 3.88, 3.18, 1.65, 1.46, 0.97.

Step 3: Methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

To an ice-cold, stirred solution of Methyl 3-bromo-5
(butylamino)-4-hydroxybenzoate (440 mg) and sodium bicarbonate
(280 mg) in 1:1 isobutyl methyl ketone/water (10 mL) was added
chloroacetyl chloride (226 mg). The mixture was stirred for 1
h, warmed to room temperature, and heated at reflux for 14 h.
The mixture was cooled to room temperature, diluted with
chloroform, and the layer separated. The organic layer was
washed with water, and brine, dried (magnesium sulfate),
filtered, and concentrated under reduced pressure to give a
white solid: ¹H NMR (300 MHz, CDCl<sub>3</sub>) & 7.94, 7.62, 4.76, 3.98,
3.93, 1.65, 1.43, 0.97, which was used in the next step
without further purification or characterization.

Step 4: A solution of the amide from step 3 and 9-BBN (780 mg) in tetrahydrofuran (10 mL) was heated at reflux for The mixture was cooled to room temperature, 1.5 h. ethanolamine (0.2 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate concentrated under reduced pressure. Purification by flash column chromatography (silica, 10% ethyl acetate/hexanes) afforded (330 mg, over 2 steps) of the title compound: 1H NMR  $(300 \text{ MHz}, \text{CDCl}_3)$   $\delta.7.55$ , 7.27, 4.36, 3.87, 3.37, 3.30, 1.60, 1.41, 0.97.

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Step 5: Methyl 4-butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

To a flask containing methyl 8-bromo-4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (0.33 g) was added NMP (7 mL), followed by copper cyanide (0.18 g). The mixture was then heated to 175 °C and stirred overnight. The resulting mixture was cooled to room temperature and poured into 1 N hydrochloric acid. The acidic aqueous layer was extracted with ethyl acetate, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided 184 mg of the title compound: ¹H NMR (300 MHz, CDCl<sub>3</sub>) δ.7.55, 7.43, 4.41, 3.89, 3.39, 3.31, 1.58, 1.40, 0.97.

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Step 6: 4-Butyl-8-cyano-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid

dihydro-2H-1,4-benzoxazine-6-carboxylate (184 mg) in methanol (3 mL) was added potassium hydroxide (7 mL of a 1.0 M solution in water). The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate.

The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and

concentrated under reduced pressure to give 154 mg of the title compound:  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.62, 7.46, 4.44, 3.41, 3.33, 1.60, 1.41, 0.98.

5 Step 7: 4-Butyl-8-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

4-Butyl-8-cyano-3, 4-dihydro-2H-1, 4-Α solution of benzoxazine-6-carboxylic acid (129 mg), HBTU (284 mg), and 10 diisopropylethylamine (0.26 mL) was stirred in methylene chloride (6 mL) for 15 min. A solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol mg) in methylene chloride (4 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with 15 methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography pressure. (silica, 1:9 methanol/chloroform) provided 20 mg of the title 20 compound: ESI MS m/z 577 [M + H]<sup>+</sup>.

EXAMPLE SP-222

 $4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-difluorobenzyl)]}$ 

25 ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxamide

Step 1: Methyl 4-nitro-3-

{[(trifluoromethyl)sulfonyl]oxy}benzoate

To an ice-cold, stirred solution of methyl 3-hydroxy-4nitrobenzoate (1.5 g) and triethylamine (1.1 mL) in methylene chloride (15 mL) was added trifluoromethane sulfonic anhydride 5 (1.4 mL), and the reaction mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided 2.4 g of the title compound: 1H NMR (300 MHz, DMSO $d_6$ )  $\delta$ , 8.47, 8.27, 8.15, 3.99.

Step 2: Methyl 3-(butylamino)-4-nitrobenzoate

$$\begin{array}{c} O_2N \\ \\ N \\ H \end{array}$$

To a stirred solution of Pd<sub>2</sub>(dba)<sub>3</sub> (139 mg), BINAP (284 mg), and cesium carbonate (2.0 g) in toluene (50 mL) was added butylamine (0.45 mL), and the reaction mixture was heated at for 15 min. A solution of methyl 4-nitro-3-{[(trifluoromethyl)sulfonyl]oxy}benzoate (1.0 g) in toluene (15 mL) was added dropwise over 1 h. The mixture was cooled 20 to room temperature, filtered through diatomaceous earth, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided 670 mg of the title compound as a yellow oil: ESI MS m/z 550 [M + H]<sup>+</sup>.

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Step 3: Methyl 4-amino-3-(butylamino)benzoate

A solution of methyl 3-(butylamino)-4-nitrobenzoate (1.1 g) and 10% Pd/C (110 mg) in methanol (20 mL) was shaken under an atmosphere of hydrogen at 50 psi for 2 h. The mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 940 mg of the title compound:  $^{1}$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.13, 6.94, 6.52, 3.72, 3.02, 1.60, 1.42, 0.93.

Step 4: Methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-610 carboxylate

To an ice-cold, stirred solution of methyl 4-amino-3-(butylamino) benzoate (950 mg) and sodium bicarbonate (862 mg) in 1:1 isobutyl methyl ketone/water (20 mL) was added chloroacetyl chloride (0.41 mL), and the mixture was stirred for 1 h. The mixture was warmed to room temperature and refluxed for 14 h. The mixture was cooled to room temperature, diluted with chloroform, and separated. The organic layer was washed with water, and brine, (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) afforded 850 mg of the title compound:  ${}^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ , 7.89, 7.72, 6.80, 3.97, 3.88, 3.30-3.25, 1.68-1.58, 1.47-1.35, 0.94-0.88.

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Step 5: Methyl 4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate

To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate (840 mg) in tetrahydrofuran (32 mL) was added borane dimethylsulfide complex (3.2 mL, 2.0 M tetrahydrofuran) and the resulting mixture was refluxed for 24 h. The mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided 364 mg of the title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.27, 7.22, 6.41, 3.84, 3.47-3.45, 3.32-3.23, 1.60-1.58, 1.42-1.37, 0.99-0.94.

Step 6: Methyl 4-butyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate

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ice-cold, stirred solution of methyl 4-butyl-To an 1,2,3,4-tetrahydroquinoxaline-6-carboxylate (180 mg) and triethylamine (62  $\mu$ L) in methylene chloride (2 mL) was added methanesulfonyl chloride (101  $\mu$ L) and the mixture was stirred The mixture was warmed to room temperature, diluted for 1 h. with methylene chloride, washed with washed with 1 N The organic layer was then hydrochloric acid, and brine. dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:3 ethyl acetate/hexanes) provided 150 mg of the title compound:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.57, 7.41, 7.32, 3.90, 3.84, 3.45, 3.38, 1.61, 1.41, 0.98.

Step 7: 4-Butyl-1-(methylsulfonyl)-1,2,3,4-

30 tetrahydroquinoxaline-6-carboxylic acid

methyl 4-butyl-1solution of stirred Tо (methylsulfonyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate added 1 M potassium in methanol (1.3 mL) was stirred at mixture was The hydroxide (13 mL). temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyle The aqueous layer was acidified to pH 4 with  $1\ N$ acetate. hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), 10 filtered, and concentrated under reduced pressure to give 99 mg of the title compound:  ${}^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.43, 7.39, 7.24, 3.77, 3.39, 3.32, 1.56, 1.33, 0.90.

15 Step 8: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(methylsulfonyl)1,2,3,4-tetrahydroquinoxaline-6-carboxamide

4-butyl-1-(methylsulfonyl)-1,2,3,4of Α solution tetrahydroguinoxaline-6-carboxylic acid (99 mg), 20 mg), HOBt (64 mg), and diisopropylethylamine (100 ML) was stirred in methylene chloride (1.0 mL) for 15 min. A solution (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3 - amino - 4 of (129 ma) ethylbenzyl)amino]butan-2-ol diisopropylethylamine (100 ML) in methylene chloride (1.0 mL) 25 was added and the mixture was stirred overnight. The mixture

was diluted with methylene chloride, washed with 1 N hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL), and brine. The organic layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure.

5 Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.5 mL, 1.0 M diethyl ether). The resulting precipitate was collected by filtration to provide 90 mg of the title compound: ESI MS m/z 629 [M + H]<sup>+</sup>.

# EXAMPLE SP-223

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-

15 tetrahydroquinoxaline-6-carboxamide hydrochloride

Step 1: 1-Tert-butyl 6-methyl 4-butyl-3-oxo-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate

To an ice-cold, stirred solution of methyl 4-butyl-3-oxo-20 1,2,3,4-tetrahydroquinoxaline-6-carboxylate (1.1)g), and triethylamine (0.9 mL) in methylene chloride (10 mL) was added DMAP (51.3 mg) and di-tert-butyl dicarbonate (1.4 g), and the The mixture was resulting mixture was stirred for 4 d. diluted with methylene chloride, washed with water, and brine. 25 dried (magnesium sulfate), The organic layer was then concentrated under pressure. filtered, and reduced Purification by flash column chromatography (silica, 1:1 ethyl

acetate/hexanes) provided 440 mg of the title compound: ESI MS m/z 363 [M + H]<sup>+</sup>.

Step 2: 1-Tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxalinei 1,6(2H)-dicarboxylate

A solution of 1-tert-butyl 6-methyl 4-butyl-3-oxo-3,4dihydroquinoxaline-1,6(2H)-dicarboxylate (440 mg) and 9-BBN dimer (600 mg) in tetrahydrofuran (10 mL) was heated at 65  $^{\circ}\mathrm{C}$ LO for 10 h. The mixture was cooled to room temperature, ethanolamine (0.15 mL) was added and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) 15 afforded 158 mg of the title compound: 1H NMR (300 MHz, CDCl3)  $\delta.7.50$ , 7.34, 7.28, 3.88, 3.77, 3.38-3.30, 1.65-1.51, 1.42-1.34, 0.99-0.94.

20 Step 3: 1-(Tert-butoxycarbonyl)-4-butyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid

To a stirred solution of 1-tert-butyl 6-methyl 4-butyl-3,4-dihydroquinoxaline-1,6(2H)-dicarboxylate (158 mg) in

methanol (1.4 mL) was added 1 M potassium hydroxide (1.4 mL). The mixture was stirred at 40 °C for 12 h and then concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 120 mg of the title compound: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.55, 7.40, 7.37, 3.79, 3.38, 3.34, 1.60, 1.53, 1.39, 0.97.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoxaline-6-carboxamide hydrochloride

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A solution of 1-(tert-butoxycarbonyl)-4-butyl-1,2,3,4tetrahydroquinoxaline-6-carboxylic acid (120 mg), HBTU (204 diisopropylethylamine (100 AL) was stirred and methylene chloride (2.0 mL) for 15 min. A solution of 20 and (146 mg) ethylbenzyl)amino]butan-2-ol diisopropylethylamine (100 AL) in methylene chloride (2.0 mL) was added and the mixture was stirred overnight. The mixture diluted with methylene chloride, washed with hydrochloric acid (10 mL), saturated sodium bicarbonate (10 25 The organic layer was then dried (magnesium mL), and brine. sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric 30

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acid (0.5 mL, 1.0 M diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide 45 mg of the title compound: ESI MS m/z 551 [M + H]<sup>+</sup>.

## 5 EXAMPLE SP-224

N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[(methylsulfonyl)methyl]nicotinamide

Step 1: Methyl 6-[(acetyloxy)methyl]nicotinate

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To a solution of methyl 6-methylnicotinate (6.05 g) in methylene chloride (100 mL) was added m-chloroperbenzoic acid (77%, 13.5 g). The reaction mixture was stirred at room temperature for 2 h and then diluted with chloroform (100 mL). 15 The mixture was washed successively with aqueous sodium sulfite, saturated sodium bicarbonate, and brine. The organic later was then dried (sodium sulfate), filtered, concentrated under reduced pressure to provide 6.21 g of methyl 6-methylnicotinate 1-oxide. A solution of methyl 6-20 methylnicotinate 1-oxide (4.35 g) in acetic anhydride (50 mL) was heated at 120 °C for 2 h and then concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 1:2 to 3:5 ethyl acetate/hexanes) provided 3.3 q of the title compound:  ${}^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  9.18, 8.31, 7.44, 5.29, 3.96, 2.19. 25

Step 3: 6-[(Methylsulfonyl)methyl]nicotinic acid

To a solution of methyl 6-[(acetyloxy)methyl]nicotinate (3.0 g) in dry methanol (100 mL) was added potassium carbonate (4.56 g). The mixture was stirred at room temperature for 2 h and then diluted with methylene chloride (200 mL) and water (200 mL). 5 The organic layer was washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.70 g of the alcohol. This material was used without further purification. To an ice-cold solution of methyl 6-(hydroxymethyl)nicotinate (1.6 g) in methylene chloride (40 mL) was added diisopropylethylamine (1.5 g) 10 followed by methanesulfonyl chloride (1.21 g). The mixture was stirred at room temperature for 1 h and then diluted with methylene chloride (100 mL). The mixture was washed successively with 0.5 N potassium hydrogen sulfate, water, and brine. The organic layer was then dried (sodium sulfate), 15 filtered, and concentrated under reduced pressure to provide mesylate 2.34 g. This mesylate was used without further purification.

To solution of methyl 6-20 {[(methylsulfonyl)oxy]methyl}nicotinate (2.34 g) in dimethylformamide (10 mL) was added sodium thiomethoxide (850 The mixture was stirred at 50 °C for 15 h. The mixture diluted with ethyl acetate (100 mL) and washed successively with water, saturated sodium bicarbonate, 25 brine. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 1.61 g of the methyl thioether. This material was used without further purification. To an ice-cold solution of methyl 6-[(methylthio)methyl]nicotinate (1.61 g) in methanol 30 (35 mL) was added a solution of oxone (7.52 g) in water (35 mL). The resulting slurry was stirred at room temperature for The resulting mixture was diluted with water (50 mL), and extracted with chloroform (3 x 100 mL). The combined organic extracts were washed with brine, dried

sulfate), filtered, and concentrated under reduced pressure to provide 1.77 g of the methyl sulfone, which was used without further purification.

То stirred solution ο£ methyl 6a 5 [(methylsulfonyl)methyl]nicotinate (800 mg) in 1:1:1 added lithium tetrahydrofuran/methanol/water (30 mL) was The mixture was hydroxide (440 mg). stirred at temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between water 10 chloroform (10 mL). The aqueous layer was acidified to pH 4 hydrochloric acid extracted with  $\mathbf{N}$ and chloroform/2-propanol  $(3 \times 30 \text{ mL})$ . The combined organic layers were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 700 mg of the title <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  9.07, 8.33, 7.65, 4.77, 15 3.06.

Step 4: N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-

20 [(methylsulfonyl)methyl]nicotinamide

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To stirred solution of 6a (181 [(methylsulfonyl)methyl]nicotinic acid mg), diisopropylethylamine (116 mg), and HBTU (341 mg) in methylene chloride (5 mL) was added a mixture of (2R,3S)-3-amino-4-(3,5difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (326 mg) and N, N-diisopropylethylamine (233 mg) in methylene chloride (5 mL). The mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate, and brine, dried (sodium sulfate),

filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5:95 to 10:90 methanol/methylene chloride) provided 165 mg of the title compound: ESI MS m/z 532 [M + H]<sup>+</sup>.

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EXAMPLE SP-225

3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-indole-5-carboxamide

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Step 1: Ethyl 4-hydrazinobenzoate hydrochloride

To a 0 °C mixture of 4-ethylaminobenzoate (10.0 g) in water (56 mL) and concentrated hydrochloric acid (20 mL) was added portion wise a solution of sodium nitrite (4.25 g) in water (20 mL). The mixture was stirred at 0 °C for 15 minutes at which time the mixture was poured into a solution of tin (II) chloride (50 gm) in water (34 mL). The resulting mixture was removed from the ice bath and allowed to slowly come to room temperature over 1 h at which time the resulting solids were collected by filtration and washed with chilled concentrated hydrochloric acid (30 mL) followed by ether. The solids were dried under vacuum to give 13 g of the title compound:  $^{1}$ H NMR (DMSO- $d_{6}$ )  $\delta$  1.29, 4.25, 7.03, 7.85, 9.0, 9.06, 10.6.

Step 2: Ethyl 3-butyl-1H-indole-5-carboxylate

To a mixture of ethyl 4-hydrazinobenzoate hydrochloride (10 gm) in ethanol: water (5:1 100 mL) was added hexanal (4.62 gm). The mixture was refluxed at 100 °C for 3 h. The solvents were removed and toluene (100 mL) and p-toluene sulfonic acid (0.1 g) were added. The mixture was refluxed at 120 °C for 18 h, cooled to room temperature and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 90:9:1 (hexanes: methylene chloride: ethyl acetate) as eluent to give 0.8 g of the title compound: ¹H NMR (CDCl<sub>3</sub>) δ 0.957, 1.44, 1.72, 2.78, 4.40, 7.02, 7.34, 7.90, 8.13, 8.38.

Step 3: Ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate

To a mixture of ethyl 3-butyl-1H-indole-5-carboxylate (0.6 g) in methylsulfoxide (10 mL) was added potassium t-butoxide (0.29 g) and iodomethane (2.0 mL). The mixture was stirred at 50 °C for 18 H, at which time the mixture was pored into water (50 mL). The solution was extracted with ethyl acetate and the organic extracts washed three times with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 5% ethyl acetate in hexanes as eluent to give 0.294 g of the title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.953, 1.44, 1.69, 2.77, 3.76, 4.40, 6.87, 7.26, 7.91, 8.35.

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Step 4: 3-Butyl-1-methyl-1H-indole-5-carboxylic acid

To a mixture of ethyl 3-butyl-1-methyl-1H-indole-5-carboxylate (0.294 g) in methanol (20 mL) was added 1N NaOH (10 mL). The mixture was stirred at 50 °C for 18 h, cooled to room, temperature and poured into 1N HCl (50 mL). The mixture was extracted with ethyl acetate and the ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.234 g (89%) of the title compound:  $^1$ H NMR (CD<sub>3</sub>OD)  $\delta$  0.965, 1.42, 1.69, 2.76, 3.77, 7.02, 7.35, 7.84, 8.29.

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Step 5: 3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1H-indole-5-carboxamide

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To a mixture of 3-Butyl-1-methyl-1H-indole-5-carboxylic acid (0.15 g) in methylene chloride (5 mL) and tetrahydrofuran (10 mL) was added 1,1-carbonyldiimidazole (0.105 g). The mixture was stirred at 40 °C at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.2 g) in methylene chloride (5 mL) was added. The mixture was stirred at 40 °C for 18 h then poured into methylene chloride (50 mL). The mixture was washed with water then brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Column chromatography on silica gel (100 mL) using 85:10:5 (methylene chloride: hexanes: methanol) as eluent to give 0.102 g of the title compound: MS (ESI+) for C<sub>33</sub>H<sub>39</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub> m/z 547.9 (M+H)<sup>+</sup>.

EXAMPLE SP-226

3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-5-carboxamide

Step 1: 3-Butyl-1H-indole-5-carboxylic acid

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To a mixture of Ethyl 3-butyl-1H-indole-5-carboxylate, EXAMPLE SP-225, step2, (0.4 g) in methanol (15 mL) was added 1N NaOH (5 mL). The mixture was stirred at 50 °C for 18 h, cooled to room temperature and poured into 1N HCl (50 mL). The mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give 0.145 g of the title compound: MS (ESI+) for  $C_{13}H_{15}N_1O_2$  m/z 216.12  $(M+H)^+$ .

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Step 2: 3-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-5-carboxamide

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To a mixture of 3-Butyl-1H-indole-5-carboxylic acid (0.145g) in methylene chloride (15 mL) was added triethylamine (0.068 g), and HATU (0.255 g). The mixture was stirred at room temperature for 15 minutes at which time (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.224 g) was added. The mixture was stirred at room temperature for 72 h then poured into methylene chloride (50 mL), washed with water then saturated sodium bicarbonate,

dried over anhydrous magnesium sulfate and concentrated under

vacuum. Column chromatography on silica gel (100 mL) using 5% methanol in methylene chloride with 0.15% HOAc as eluent to give 0.247 g of the title compound: MS (ESI+) for  $C_{32}H_{37}F_2N_3O_2$  m/z 534.3 (M+H)<sup>+</sup>.

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EXAMPLE SP-227

4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

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Step 1: Methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

To an ice-cold, stirred solution of methyl 3-amino-4-15 hydroxybenzoate (3.0 g) and sodium bicarbonate (3.3 g) in 1:1 isobutyl methyl ketone/water (40 mL) was added chloroacetyl chloride (1.7 mL), and the mixture was stirred for 1 h. mixture was warmed to room temperature and refluxed for 14 h, cooled to room temperature, diluted with chloroform, 20 separated. The organic layer was washed with water, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column pressure. chromatography (silica, 1:9 methanol/chloroform) afforded a phenoxazine 3.2 g as a white solid, which was used without 25 further purification or characterization. To a solution of phenoxazine from step 1 (700 mg) and potassium carbonate (934 mg) in methanol (8 mL) was added bromobutane (1.8 mL), and the mixture was refluxed for 6 d. The mixture was cooled to room temperature, concentrated under reduced pressure, and the 30 residue was partitioned between ethyl acetate and water. organic layer washed with brine, dried (magnesium sulfate),

filtered, and concentrated under reduced pressure to afforded 800 mg of the title compound:  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ .7.72-7.68, 7.02-6.99, 4.66, 4.00-3.92, 1.69-1.64, 1.46-1.38, 1.01-0.95.

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Step 2: Methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate

A solution of methyl 4-butyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (800 mg) and 9-BBN (1.6 g) in tetrahydrofuran (13 mL) was refluxed for 1.5 h. The mixture was cooled to room temperature, ethanolamine (0.4 mL) was added, and the resulting solution was concentrated under reduced pressure. The residue was washed with hexanes, filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (silica, 25% ethyl acetate/hexanes) afforded 607 mg of the title compound: <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.21, 7.16, 6.75, 4.24-4.21, 3.78, 3.34-3.24, 1.55-1.47, 1.38-1.30, 0.95-0.90.

Step 3: 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylic acid

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To a stirred solution of methyl 4-butyl-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate (412 mg) in methanol (5 mL) was added 1 M potassium hydroxide (17 mL). The mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was diluted with water and

washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform  $(4 \times 50 \text{ mL})$ . The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 384 mg of the title compound: ESI MS m/z 236 [M + H]<sup>+</sup>.

Step 4: 4-Butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide

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A solution of 4-Butyl-3,4-dihydro-2H-1,4-benzoxazine-6carboxylic acid (43 mg), HATU (104 mg), HOBt (37 mg), and diisopropylethylamine (47 □L) was stirred in methylene chloride (1.0 mL) for 15 min. A solution of (2R,3S)-3-amino-15 4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (62 mg) and diisopropylethylamine (47 □L) in methylene chloride (1.0 mL) was added and the reaction mixture was stirred overnight. The mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (15 mL), saturated sodium bicarbonate (15 mL), and brine, dried (magnesium 20 sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, methanol/chloroform) provided 15 mg of the title compound: APCI MS m/z 552 [M + H]<sup>+</sup>.

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## EXAMPLE SP-228

3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide

30 Step 1. Methyl 1-butyl-1H-indole-6-carboxylate

Methyl 1H-indole-6-carboxylate (4.17g) was dissolved in DMSO (30 mL), and potassium tert-butoxide (2.93 g) was added. The mixture was stirred for ten min at room temperature.

5 Iodobutane (3.0 mL) was added. The mixture was allowed to stir for three additional hours. The mixture was partitioned between ethyl acetate and water and brine, dried over sodium sulfate, filtered, and concentrated to give methyl 1-butyl-1H-indole-6-carboxylate (4.53 g). MS (ESI+) for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>+H<sub>1</sub> m/z 232.12 (M+H)<sup>+</sup>.

Step 2. Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate

1-butyl-1H-indole-6-carboxylate (4.53 dissolved in dichloromethane (25ml). The mixture was cooled Diethyl aluminum chloride was added dropwise (29.5 to 0 °C. mL) and the mixture was allowed to stir at 0 °C for 30 min. A solution of dichloromethane (25 mL) and acetyl chloride (2.1 mL) was added dropwise, and the mixture was stirred for 2 h at 20 °C. The mixture was then partitioned dichloromethane, water, and brine, dried over sodium sulfate, concentrated. The filtered. and concentrate chromatographed on silica gel using ethyl acetate/heptane methyl 3-acetyl-1-butyl-1H-indole-6-(40/60)to give 25 carboxylate (3.38 g). MS (ESI+) for  $C_{16}H_{19}N_1O_3+H_1$  m/z 274.14  $(M+H)^+$ .

Step 3. 3-acetyl-1-butyl-1H-indole-6-carboxylic acid

Methyl 3-acetyl-1-butyl-1H-indole-6-carboxylate (2.00 g) was dissolved in methanol (100mL). Sodium hydroxide (1N) was added until the mixture became slightly cloudy. Methanol was again added (20 mL) until the solution was clear. hydroxide was again added until the mixture was slightly cloudy. The mixture was allowed to stir at room temperature The solution was concentrated to half its original overnight. volume and hydrochloric acid (2N) was added until the aqueous layer indicated a pH of about one. The mixture was extracted 10 with dichloromethane and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting material was chromatographed on silica gel using MeOH/heptane/dichloromethane (4/20/76) to give 3-acetyl-1butyl-1H-indole-6-carboxylic acid (1.60 g). 15 MS (ESI+) for  $C_{15}H_{17}N_1O_3+H_1 m/z 260.13 (M+H)^+$ 

Step 4.  $3-acetyl-1-butyl-N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-$ 

20 carboxamide

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3-Acetyl-1-butyl-1H-indole-6-carboxylic acid (0.322 g) was dissolved in dichloromethane (15 mL). 1,1'-Carbonyldiimidazole was added (0.171 g). The mixture was stirred for 2 h and then a mixture of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (0.250 g) in dichloromethane (15 mL) was added. After stirring

overnight, the mixture was partitioned between dichloromethane, water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using MeOH/dichloromethane (4/96) to give 3-acetyl-1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide (0.335 g). MS (ESI+) for C<sub>34</sub>H<sub>39</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub>+H<sub>1</sub> m/z 576.30 (M+H)<sup>+</sup>.

## 10 EXAMPLE SP-229

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1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide

15 Step 1. Butyl 1-butyl-1H-indole-6-carboxylate

1-Butyl-1H-indole-6-carboxylic acid (0.450)a) was dissolved in dimethyl sulfoxide (10mL). Potassium tertbutoxide (0.317 g) was added and the mixture was stirred for 10 min at room temperature. Iodobutane (0.33 mL) was added and the mixture was allowed to stir at room temperature for 6 h. Water was then added and the mixture was partioned between ethyl acetate, water, and brine, and dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography using heptane/dichloromethane (30/70)butyl 1-butyl-1H-indole-6-carboxylate (0.429 g). for  $C_{17}H_{23}NO_2 + H_1 m/z 274.20 (M+H)^+$ .

Step 2. Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-30 carboxylate

Boron trifluoride-methyl sulfide complex (0.238 g) was dissolved in dichloromethane (10 mL). The solution was cooled to -78 °C and a solution of trifluoroacetic anhydride (0.384 g) in dichloromethane (2 mL) was added. The mixture was stirred at -78 °C for 10 min, at which time a solution of butyl 1butyl-1H-indole-6-carboxylate (0.250 g) in dichloromethane (3 mL) was added. The mixture was allowed to stir at -78 °C for 15 min and then allowed to warm to room temperature overnight. The mixture was then poured into aqueous sodium bicarbonate 10 and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and concentrated and the resulting material was chromatographed on silica gel using ethyl acetate/heptane (20/80) to give butyl 1-buty1-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.302 15 g). (ESI+) for  $C_{19}H_{22}F_3N_1O_3+H_1 m/z 370.16 (M+H)^+$ .

Step 3. 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid

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Butyl 1-butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylate (0.277~g), LiOH•H<sub>2</sub>O (0.040~g), THF (1.5~mL), water (0.5~mL), and methanol (0.5~mL) were stirred overnight at room temperature. The solvents were then removed under reduced pressure and HCl (2N,~0.5mL) was added to the residue. The residue was extracted with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated. Chromatography on silica

gel using methanol/dichloromethane (6/94) gave 1-butyl-3- (trifluoroacetyl)-1H-indole-6-carboxylic acid (0.166 g). MS (ESI+) for  $C_{15}H_{14}F_{3}N_{1}O_{3}+H_{1}$  m/z 314.10 (M+H)<sup>+</sup>.

5 Step 4. 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1H-indole-6-carboxamide

1-Butyl-3-(trifluoroacetyl)-1H-indole-6-carboxylic acid (0.141 g) was dissolved in dichloromethane (10 mL). 10 Carbonyldiimidazole (0.080 g) was added and the mixture was stirred at room temperature for 2 h. A solution of (2R,3S)-3amino-4-(3.5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2ol (0.166 g) in dichloromethane was added and the mixture was allowed to stir overnight at room temperature. The mixture 15 was then partitioned between dichloromethane and water, dried sodium sulfate, filtered, and concentrated. over silica gel using methanol/ethyl Chromatography on acetate/heptane /dichloromethane (3/10/10/77 to 6/10/10/74)  $1-butyl-N-{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-difluorobenzyl)]}$ 20 gave ethylbenzyl)amino]-2-hydroxypropyl}-3-(trifluoroacetyl)-1Hindole-6-carboxamide (0.155 g). MS (ESI+) for  $C_{34}H_{36}F_5N_3O_3+H_1$ m/z 630.28 (M+H)<sup>+</sup>.

25 EXAMPLE SP-230

N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2(dipropylamino)isonicotinamide

2-(Dipropylamino)isonicotinic acid (0.206 g) was dissolved in dichloromethane (10 mL). 1,1'-Carbonyldiimidazole was added (0.142 g) and the mixture was stirred for 2 h at room temperature, at which time (2R,3S)-3 $amino-4-(3,5-difluorophenyl)-1-{[1-(3$ ethynylphenyl)cyclopropyl]amino}butan-2-ol (0.284)g) in dichloromethane was added. The mixture was allowed to stir overnight and then was partitioned between dichloromethane, water, and brine, dried over sodium sulfate, filtered, concentrated under reduced pressure. The concentrate was chromatographed on silica gel using methanol/dichloromethane

15 (dipropylamino)isonicotinamide (0.268g). MS (ESI+) for  $C_{33}H_{38}F_2N_4O_2+H_1$  m/z 561.30 (M+H)<sup>+</sup>.

 $N-((1S, 2R)-1-(3, 5-difluorobenzy1)-3-\{[1-(3-$ 

# EXAMPLE SP-231

to

give

(4/96)

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 $1-butyl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-4)]}$ 

ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-

20 ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-1H-indole-6-carboxamide

In the same manner as for N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-(dipropylamino)isonicotinamide, 1-butyl-1H-indole-6-carboxylic acid (0.119 g) gave 1-butyl-N-((1S,2R)-1-

 $(3,5-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-\{[1-(3-difluorobenzyl)-3-[1-difluorobenzyl]-3-[1-difluorobenzyl]-3-[1-difluorobenzyl]-1-difluorobenzyl]-1-difluorobenzyl]$ carboxamide (0.076g). MS (ESI+) for C34H35F2N3O2+H1 m/z 556.28 (M+H))^+.

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# EXAMPLE SP-231

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

- 3-Thiobenzoic acid (Aldrich, 4.3g, 28mmol) was dissolved in THF (100mL), cooled to 0°C, and treated with KO-tBu (6.3g, 56mmol), followed by allyl bromide (2.4mL, 28mmol). The solvent was removed from the reaction mixture and the residue was partitioned between 3M HCl and EtOAc. The organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated to give the title compound (5.3g). (LRMS (M-H) m/z 193.2)
- Step 2. 3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)
  3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2hydroxypropyl)benzamide
  - 3-(Allylthio)benzoic acid (717mg, 3.69mmol), (2R,3R)-3-amino-4-(3,5-difluorophenyl)-1-{[1-(3-
- 25 ethylphenyl)cyclopropyl]amino}butan-2-ol (247mg, 0.685mmol), and HATU (Aldrich, 2.1g, 5.54mmol) were dissolved dichloromethane (35mL), at ambient temperature, and treated with diisopropylethylamine (1.6mL, 9.225mmol). Upon completion, the reaction mixture was concentrated and 30 chromatographed (SiO2, 2:1 to 1:1 Hexanes: EtOAc) to give the desired compound (650mg). (LRMS (M+H) m/z = 537.8)

EXAMPLE SP-232

3-(allylsulfinyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide (325mg, 0.606mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10mL) and AcOH (1mL)and treated with mCPBA (104mg, 0.606mmol). The reaction mixture was stirred for 2.5h, at which time more mCPBA (20mg, 0.11mmol) was added and stirring continued for 30 min. more.

10 The organic layer was diluted with Et<sub>2</sub>O and washed with 15% sodium thiosulfite solution. The organic was washed with brine, then dried (MgSO<sub>4</sub>) and concentrated to give an oil, which was chromatographed with 25% to 50%EtOAc in hexanes to give the title compound. (LRMS (M+H) m/z 553.8)

#### EXAMPLE SP-233

3-(allylsulfonyl)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide

3-(allylthio)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamide (245mg, 0.456mmol) was dissolved in MeOH:H<sub>2</sub>O (9:1, 6mL) and treated with oxone (561mg, 0.913mmol). When the reaction was complete, the mixture was concentrated to 0.5x volume and poured onto EtOAc. This was washed with a 15% sodium thiosulfite solution, dried (MgSO<sub>4</sub>) and concentrated to give the title compound. (LRMS (M+H) m/z 569.8)

## EXAMPLE SP-234

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide

Step 1. 2-chloro-6-methylisonicotinonitrile

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Using the method of Org. Prep. Proceed. Intern. (1982) 396, 2-chloro-6-methylisonicotinic acid (0.405 g, 2.36 mmol) was converted to 2-chloro-6-methylisonicotinonitrile (0.241 g).

Step 2. 2-(dipropylamino)-6-methylisonicotinonitrile

$$C = N$$

$$C = N$$

$$C = N$$

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To 2-chloro-6-methylisonicotinonitrile (0.230 g, 1.51 mmol) was added di-n-propylamine (5 mL). The mixture was heated at 80 °C in a sealed, thick-walled glass vessel for 12 h and then at room temperature for 17 h. Excess di-n-

propylamine was removed under reduced pressure and the residue partitioned between dichloromethane and aq. sodium sulfate and After drying over sodium bicarbonate. concentration, the residue was chromatographed on silica gel using ethyl acetate-hexane (10/90) to give 0.14 g of 2-chloro-6-methylisonicotinonitrile and 0.059 g of 2-(dipropylamino)-6methylisonicotinonitrile. Using the above conditions, chloro-6-methylisonicotinonitrile (0.14 g) was converted to an 2-(dipropylamino)-6-0.043 of additional g methylisonicotinonitrile.

Step 3. 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride

To 2-(dipropylamino)-6-methylisonicotinonitrile (0.094 g, 0.433 mmol) was added 4N HCl (2 mL) and THF (1 mL). 15 mixture was stirred at 100 °C (THF allowed to distill off) for layer was removed under reduced 12 h, then the aqueous and using a toluene azeotrope to pressure (dipropylamino)-6-methylisonicotinic acid hydrochloride, which was used without further purification in the next step. 20

Step 4. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide

To 2-(dipropylamino)-6-methylisonicotinic acid hydrochloride (approx. 0.4 mmol) in THF (3 mL) was added

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triethylamine (0.17 mL), followed by dichloromethane (2 mL) and then CDI (0.071 g, 0.44 mmol). After stirring for 1 h, a mixture of (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4ethylbenzyl)amino]butan-2-ol dihydrochloride (0.163 g, 0.400 mmol), triethylamine (0.11 mL), and dichloromethane (approx. 2 mL) was added to the CDI mixture. The mixture was allowed to stir overnight, after which an additional 0.12 triethylamine and 0.045 g of (2R, 3S) - 3 - amino - 4 - (3, 5 - 3)difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol

10 dihydrochloride was added. After stirring for several more hours, the mixture was partitioned between dichloromethane and aq. sodium bicarbonate. The organic layer was dried with sodium sulfate, concentrated, and the residue chromatographed on silica gel using MeOH-dichloromethane 15 (5/95) to give 0.04 g of the title compound.

## EXAMPLE SP-235

 $N-\{(1S,2R)-1-(3,5-\text{difluorobenzyl})-3-[(3-\text{ethylbenzyl})\,\text{amino}]-2-hydroxypropylluorobenzyl)-6-methylpyrimidine-4-$ 

20 carboxamide

Step 1. methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate

A mixture of methyl 2-chloro-6-methylpyrimidine-4-carboxylate (0.411 g, 2.20 mmol), di-n-propylamine (0.668 g, 6.60 mmol), triethylamine (0.267 g, 2.64 mmol), and THF (5 ml) was stirred at room temperature for 55 min and then at reflux for 1.3 h, at which time is was cooled and partitioned between ethyl acetate and a mixture of brine and aq. sodium bicarbonate. The organic layer was dried over magnesium

sulfate and concentrated and then chromatographed on silica gel using ethyl acetate-hexane (90/10) to give methyl 2-(dipropylamino)-6-methylpyrimidine-4-carboxylate (0.457 g) as a pale yellow liquid.

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Step 2. 35137-ret-135 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid

2-(dipropylamino)-6-methylpyrimidine-4methyl To carboxylate (0.450 g, 1.79 mmol) in MeOH (2 mL), water (1 mL), 10 and THF (1 mL) was added lithium hydroxide monohydrate (0.113 The mixture was stirred at room temperature q, 2.68 mmol). for 1 h and then MeOH and THF were removed under reduced The pH of the residue was adjusted to approximately pressure. resulting mixture was extracted the 15 and dichloromethane, dried over sodium sulfate, and concentrated to give 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid (0.351 g) as a yellow solid.

20 Step 3. N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide

To 2-(dipropylamino)-6-methylpyrimidine-4-carboxylic acid 25 (0.101 g, 0.426 mmol) in THF (0.5 mL) was added 1,1'-carbonyldiimidazole (CDI) (0.076 g, 0.468 mmol). After 50 min the CDI mixture was added to a mixture of (2R,3S)-3-amino-4-

(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (0.173 g, 0.425 mmol) and triethylamine (0.18 mL, 1.28 mmol) in THF (6 mL) and dichloromethane (2 mL). After stirring overnight, the solvents were removed under reduced pressure and the residue was partitioned between dichloromethane, aq. sodium bicarbonate, and aq. bicarbonate-brine mixture. The organic layer was dried over concentrated, and the residue sulfate, sodium chromatographed on silica gel using MeOH-dichloromethane (5/95) to give 0.199 g of the title compound as a solid.

## EXAMPLE SP-236

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3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}imidazo[1,2-a]pyridine-6-carboxamide

Step 1. 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid

To hexanal (1.02 g, 10.2 mmol) in 15 mL of isopropyl alcohol-water (4:1 v/v) was added  $\text{CuCl}_2$  (1.37 g, 10.2 mmol). The mixture was heated at 80 °C for 2.5 h, then cooled. 20 solids were removed by filtration and the filtrate was added to 6-aminonicotinic acid (1.35 g, 10 mmol). The mixture was stirred overnight at room temperature, then heated at reflux 32 h. After cooling, the solvents were removed under reduced pressure and MeOH was added to the residue. The resulting 25 solid was removed by filtration and the filtrate MeOH was again added, and the concentrated to dryness. resulting solid removed by filtration. After concentration of the filtrate, the residue was chromatographed on silica gel using MeOH-dichloromethane (33/67) to give 0.26 g of 3-30 butylimidazo[1,2-a]pyridine-6-carboxylic acid.

3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}imidazo[1,2-a]pyridine-6-carboxamide

5 Step 2. In the  $N-\{(1S, 2R)-1-(3, 5$ same manner as for difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-SP-235}, Step 3, 3-butylimidazo[1,2-a]pyridine-6-carboxylic acid (0.16 g) was converted to 0.30 g of the title compound.

EXAMPLE SP-237

2-[butyl(methyl)amino]-6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide

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Step 1. methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate

In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide {EXAMPLE SP-234, Step 2,} methyl 2,6-dichloroisonicotinate (1.0 g) was converted to methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.87 g).

Step 2. 2-[butyl(methyl)amino]-6-chloroisonicotinic acid

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for  $N-\{(1S,2R)-1-(3,5-$ In the same manner as difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-5 2435}, Step methyl 2-[butyl(methyl)amino]-6-(0.17 chloroisonicotinate g) was converted to 2-[butyl(methyl)amino]-6-chloroisonicotinic acid (0.15 g).

10 Step 3. 2-[butyl(methyl)amino]-6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide

$$\begin{array}{c} CI \\ N \\ OH \end{array} \longrightarrow \begin{array}{c} CI \\ NH \\ OH \end{array} \longrightarrow \begin{array}{c} OH \\ NH \\ OH \end{array}$$

In the for  $N-\{(1S,2R)-1-(3,5$ same manner as 15 difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino) -6-methylpyrimidine-4-carboxamide {EXAMPLE 2435}, 3, 2-[butyl(methyl)amino]-6-chloroisonicotinic Step acid (0.15 g) was converted to 0.13 g of the title compound.

- 20 EXAMPLE SP-238
  2-[butyl(methyl)amino]-6-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide
- 25 Step 1. methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate

A flask containing methyl 2-[butyl(methyl)amino]-6-chloroisonicotinate (0.306 g, 1.19 mmol), zinc cyanide (0.0839 g, 0.714 mmol), Pd<sub>2</sub>dba<sub>3</sub> (0.0218 g, 0.024 mmol), dppf (0.0264 g, 0.048 mmol), and zinc dust (0.0093 g, 0.143 g) was flushed with nitrogen. N-Methylpyrrolidinone (2 mL) was added and the mixture was heated at 120 °C for 2 h, at which time it was cooled and partitioned between ethyl acetate and aq. ammonium hydroxide and brine. The organic layer was dried over magnesium sulfate and concentrated, followed by silica get chromatography using ethyl acetate-hexane (10/90) to give 0.161 g of methyl 2-[butyl(methyl)amino]-6-cyanoisonicotinate.

Step 2. 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid

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 $N-\{(1S, 2R)-1-(3, 5$ for In the same manner as difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE 2-[butyl(methyl)amino]-6-Step 2435}, ,methyl converted to 2cyanoisonicotinate (0.157)g) was [butyl(methyl)amino]-6-cyanoisonicotinic acid (0.151 g).

Step 3. 2-[butyl(methyl)amino]-6-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide

In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzyl)amino]-2-hydroxypropy1}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-[butyl(methyl)amino]-6-cyanoisonicotinic acid (0.135 g) was converted to the title compound (0.223 g).

EXAMPLE SP-239

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2-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-10 ethylbenzyl)amino]-2-hydroxypropyl}-6-[methyl(propyl)amino]isonicotinamide

In the same manner as for N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylpyrimidine-4-carboxamide {EXAMPLE S-2435}, Step 3, 2-cyano-6-[methyl(propyl)amino]isonicotinic acid (0.13 g) gave 0.23 g of the title compound.

20 EXAMPLE SP-240

Reaction scheme for the preparation of 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroquinoline-7-carboxamide

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Step 1: To an ice-cold, stirred solution of quinolin-7-ol (1.0 g, 6.9 mmol) and triethylamine (1.0 mL, 7.6 mmol) in methylene chloride (14 mL) was added trifluoromethane sulfonic anhydride (1.3 mL, 7.6 mmol), and the mixture was stirred for 30 min. The mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and brine, dried (magnesium sulfate), filtered, and concentrated under reduced pressure provided quinolin-7-yl trifluoroacetate (1.5 g): ESI MS m/z 278 [M + H]\*.

Step 2: To a stirred solution of quinolin-7-yl trifluoroacetate (750 mg, 2.7 mmol),  $PdCl_2(Ph_3P)$  (95 mg, 0.14 mmol), and triethylamine (1.2 mL, 8.4 mmol) in 1:2 DMF/MeOH

(39 mL) was degassed and sparged with CO, and the mixture was The mixture was cooled to room heated at 60 °C for 48 h. through and temperature, filtered diatomaceous earth, concentrated under reduced pressure. The residue was diluted with a 5% solution of LiCl, and washed with  $CHCl_3$  (3 x 250 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated under reduced pressure. Purification by flash column chromatography (silica, 3:1 ethyl acetate/hexanes) provided methyl quinoline-7-carboxylate (185 mg): ESI MS m/z  $188 [M + H]^{+}$ .

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- Step 3: A solution of methyl quinoline-7-carboxylate (185 mg, 1.0 mmol) and PtO<sub>2</sub> (20 mg) in methanol (10 mL) was shaken under an atmosphere of hydrogen for 2 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide methyl 1,2,3,4-tetrahydroquinoline-7-carboxylate (189 mg): ESI MS m/z 192 [M+H]<sup>+</sup>.
- solution of methyl 1,2,3,4-20 To a stirred Step tetrahydroquinoline-7-carboxylate (180 mg, 0.94 mmol) cesium bicarbonate (1.5 g, 4.7 mmol) in THF (2 mL) was added n-butyl bromide (1.0 mL, 9.4 mmol), and the reaction mixture was heated at reflux for 48 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc. The 25 organic layer was washed with water, and brine, (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography pressure. (silica, 1:3 ethyl acetate/hexanes) afforded methyl 1-butyl-30 1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg): ESI MS m/z  $248 [M + H]^{+}$ .
  - Step 5: To a stirred solution of methyl 1-butyl-1,2,3,4-tetrahydroquinoline-7-carboxylate (156 mg, 0.63 mmol) in

methanol (1.3 mL) was added potassium hydroxide (6.3 mL of a 1 M solution in water, 6.3 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid and extracted with chloroform The combined organic extracts were dried  $(4 \times 100 \text{ mL}).$ (sodium sulfate), filtered, and concentrated under reduced Purification by flash column pressure. chromatography (silica, 1:9 methanol/chloroform) afforded 1-butyl-1,2,3,4-10 tetrahydroquinoline-7-carboxylic acid (139 mg): ESI MS m/z 234  $[M + H]^+$ .

- Step 6: A solution of 1-buty1-1,2,3,4-tetrahydroquinoline-715 carboxylic acid (134 mg, 0.57 mmol), HBTU (327 mg, 0.86 mmol),
  and diisopropylethylamine (150 μL, 0.86 mmol) was stirred in
  methylene chloride (3.0 mL) for 15 min. A solution of
  (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3ethylbenzyl)amino]butan-2-ol (EXAMPLE SP-272) (234 mg, 0.57
  20 mmol) and diisopropylethylamine (150 μL, 0.86 mmol) in
  methylene chloride (3.0 mL) was added and the reaction mixture
  was stirred overnight. The reaction mixture was diluted with
- saturated sodium bicarbonate (10 mL), and brine. The organic

  layer was then dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided 1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-

methylene chloride, washed with 1 N hydrochloric acid (10 mL),

30 tetrahydroquinoline-7-carboxamide (130 mg): ESI MS m/z 550 [M + H]<sup>+</sup>

## EXAMPLE SP-241

 $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-3-propyl-1,2-benzisoxazole-5-carboxamide$ 

General Synthesis of Benzisoxazole

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Furan 1 was hydrogenated to afford amine 2. Diels-Alder reaction of amine 2 and 1-hexen-3-one afforded ketone 3. 1 Ketone 3 was then treated with p-toluenesulfonic acid to afford diketone 4. Diketone 4 was rearomatized with boron trifluoride to give phenol 5. Phenol 5 was then converted to oxime 6 with hydroxylamine. Oxime 6 was cyclized with thionyl chloride to afford methyl ester 7. 2 Methyl ester 7 was then saponified to acid 8. Coupling of acid 8 and amine 9 in the presence of HATU, provided benzoxazole 10.

Reaction scheme

 $N-\{(1S,2R)-1-(3,5-diffluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1\}-3-propy1-1,2-benzisoxazole-5-carboxamide$ 

5 Step 1: A mixture of methyl 5-nitro-2-furoate (13 g, 76 mmol) and 10% Pd/C (1.3 g) in ethanol (150 mL) was shaken under an atmosphere of hydrogen at 40 psi for 18 h. The reaction mixture filtered was through diatomaceous earth and concentrated under reduced pressure to afford a crude oil. 10 Purification by flash column chromatography (silica, hexanes/ethyl acetate) provided methyl 5-amino-2-furoate (5.6 g):  $^{1}$ H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ 7.11-7.10 (m, 1H), 5.31-5.29 (m, 1H), 4.31 (br s, 2H), 3.84 (s, 3H).

Step 2: A stirred solution of methyl 5-amino-2-furoate (1.4 g, 10 mmol) and 1-hexen-3-one (7 mL, 60 mmol) in benzene (50 mL) was heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 2:1 hexanes/ethyl acetate) provided methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  6.26-6.23 (m, 1H), 6.09-6.05 (m, 1H), 3.80 (s, 3H), 3.02-2.96 (m, 1H), 2.89-2.84 (m, 1H), 2.42-2.37 (m, 2H), 1.64-1.57 (m, 2H), 0.96-0.88 (m, 3H).

Step 3: To a stirred solution of methyl 4-amino-5-butyryl-1-hydroxycyclohexa-2,4-diene-1-carboxylate (1.25 g, 5.2 mmol) in a 1:1 mixture of water/tetrahydrofuran (10 mL) was added ptoluenesulfonic acid monohydrate (1.1 g, 5.8 mmol). The reaction mixture was stirred for 18 h and then partitioned between dichloromethane and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 5-butyryl-1-hydroxy-4-oxocyclohex-2-ene-1-carboxylate which was used without further purification or characterization.

Step 4: To a stirred solution of methyl 5-butyryl-1-hydroxy-425 oxocyclohex-2-ene-1-carboxylate in benzene was added BF<sub>3</sub>·O(Et)<sub>2</sub>
(1.3 mL, 10 mmol). The mixture was stirred for 0.25 h and then quenched with saturated sodium bicarbonate followed by extraction with dichloromethane. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 3-butyryl-4-hydroxybenzoate which was used without further purification or characterization.

Step 5: A stirred solution of methyl 3-butyryl-4-hydroxybenzoate, pyridine (3.7 mL, 46 mmol), and hydroxylamine

hydrochloride (3.55 g, 51 mmol) in ethanol (30 mL) was heated reflux for 2 h. The mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, 10:1 hexanes/ethyl acetate) provided methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg): <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): 8 8.30-8.28 (m, 1H), 7.85-7.82 (m, 1H), 6.92-6.89 (m, 1H), 3.88 (s, 3H), 2.87-2.84 (m, 2H), 1.67-1.60 (m, 2H), 1.05-1.00 (m, 3H).

Step 6: To an ice-cold stirred solution of methyl 4-hydroxy-3-[(1E)-N-hydroxybutanimidoyl]benzoate (170 mg, 0.7 mmol) 15 diethyl ether (5 mL) was added a mixture of thionyl chloride (60  $\mu$ L, 0.8 mmol) and pyridine (580  $\mu$ L, 7.2 mmol) in diethyl ether (5 mL). After 2.5 h the mixture was poured over icewater and acidified to pH = 1 with 1 N hydrochloric acid. mixture was then partitioned between water and ethyl acetate. 20 The organic layer was washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column chromatography (silica, acetate) provided methyl 3-propyl-1,2-25 hexanes/ethyl benzisoxazole-5-carboxylate (90 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ 8.36-8.35 (m, 1H), 8.07-8.04 (m, 1H), 7.52-7.49 (m, 1H), 3.95(s, 3H), 2.96-2.91 (m, 2H), 2.00-1.87 (m, 2H), 1.09-1.04 (m, 2H), 1.09-1.043H).

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Step 7: To a solution of methyl 3-propyl-1,2-benzisoxazole-5-carboxylate (90 mg, 0.4 mmol) in a 2:1:1 mixture of tetrahydrofuran, water, and methanol (4 mL) was added lithium hydroxide (50 mg, 1.2 mmol) and the resulting reaction mixture

stirred at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure, and partitioned between water and ethyl ether. The aqueous layer was washed twice with ether and acidified to pH 1 with 6 M hydrochloric The resulting aqueous layer was extracted with ethyl acid. dried (sodium sulfate), and concentrated under afford 3-propyl-1,2-benzisoxazole-5pressure to reduced carboxylic acid (73 mg):  $^{1}$ H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.28-8.27 (m, 1H), 8.09-8.06 (m, 1H), 7.64-7.61 (m, 1H), 2.99-2.94 (m, 1H)2H), 1.96-1.86 (m, 2H), 1.08-1.02 (m, 3H).

Step 8: To a stirred solution of 3-propyl-1,2-benzisoxazole-5carboxylic acid (70 mg, 0.3 mmol) and HATU (130 mg, 0.3 mmol) chloride (5 mL) was added N, Nin methylene diisopropylethylamine (110 µL, 0.6 mmol). In a separate flask, 15 N, N-diisopropylethylamine (110  $\mu$ L, 0.6 mmol) was added to (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]] - 1 - [(3 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - amino - 4 - amino - 4 - (3 - amino - 4 - amethylbenzyl)amino]butan-2-ol (EXA xxx) (140 mg, 0.3 mmol) in methylene chloride (2 mL). This solution was added to the above solution containing the acid and the resulting reaction 20 mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride The organic layer was washed with water, dried and water. (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column 25 chromatography (silica, gradient 97:3 to 94:6 methylene chloride/methanol) provided N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-propyl-1,2benzisoxazole-5-carboxamide (30 mg). ESI-MS m/z 522 [M + H]<sup>+</sup>

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EXAMPLE SP-242

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide dihydrochloride

Step 1: A solution of 7-bromo-1-chloroisoquinoline (2.50 g, 10.3 mmol) and activated zinc (1.40 g, 21.65 mmol) in acetic acid (20 mL) was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 7-bromoisoquinoline (1.86 g): ESI MS m/z 208 [M + H]<sup>+</sup>.

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Step 2: A solution of 7-bromoisoquinoline (1.80 g, 8.65 mmol) and cuprous cyanide (1.16 g, 12.97 mmol) in pyrrolidinone (17 mL) was heated to 200 °C for 2 h. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. phase was back-extracted with additional ethyl acetate and the combined organic layers were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-cyano-isoquinoline (770 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 9.35 (s, 1H), 8.70 (d, J = 5 Hz, 1H),

8.40 (s, 1H), 7.95 (d, J = 8 .Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.73 (d, J = 5 Hz, 1H); ESI MS m/z 155 [M + H]<sup>+</sup>.

Step 3: A solution of 7-cyanoisoquinoline (770 mg, 5.0 mmol) in concentrated hydrochloric acid (25 mL) was heated in a sealed tube to 150 °C for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and neutralized to pH 7.0 with concentrated ammonium hydroxide.

10 The solution was vacuum filtered and the filtrate concentrated under reduced pressure to provide isoquinoline-7-carboxylic acid (640 mg): ESI MS m/z 174 [M + H]<sup>+</sup>.

Step 4: To a stirred solution of isoquinoline-7-carboxylic acid (200 mg, 1.15 mmol) and N,N-diisopropyl ethylamine (1.20 mL, 6.88 mmol) in methylene chloride (14.0 mL) was added HBTU (438 mg, 1.15 mmol) and the reaction stirred for 0.5 h. (2R,3S)-3-Amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol (470 mg, 1.15 mmol) was added in one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure.

25 Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

hydroxypropyl}isoquinoline-7-carboxamide (100 mg) which was characterized as its bis-HCl salt: mp 142-143 °C; ESI MS m/z

 $30 490 [M + H]^+$ 

EXAMPLE SP-243

N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamide dihydrochloride

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Step 1: A solution of 7-bromo-1-chloroisoquinoline in propylamine (15.0 mL) was heated at 70 °C in a sealed tube overnight. The reaction mixture was concentrated under reduced pressure, then dissolved in chloroform and washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield 7-bromo-2-(N-propylamino)isoquinoline (820 mg): ESI MS m/z 266 [M + H]<sup>+</sup>

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Step 2: A solution of 7-bromo-2-(N-propylamino)isoquinoline (200 mg, 0.754 mmol) in anhydrous diethyl ether (1.0 mL) was cooled to -65 °C. To this solution sec-butyllithium was added dropwise (1.30 mL of a 1.3 M solution in cyclohexane, 1.69 mmol) and the reaction mixture stirred at -60 °C for 10 min. The reaction mixture was quenched by addition of pulverized dry ice ( $CO_2$ ) and the reaction allowed to slowly warm to room temperature over 1 h. The resulting solution was acidified

with 1 N hydrochloric acid and the reaction mixture extracted with ethyl acetate  $(3 \times 15 \text{ mL})$ . The combined organic phase was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown solid. Purification flash by column chromatography (silica, 66:20:10:4 ethyl acetate/chloroform/methanol/concentrated ammonium hydroxide) gave 1-(propylamino)isoquinoline-7carboxylic acid (133 mg): ESI MS m/z 231 [M + H]<sup>+</sup>.

10 Step 3: To a stirred solution of 1-(propylamino)isoquinoline-7-carboxylic acid (81 mg, 0.396 mmol) and N,N-diisopropyl ethylamine (3.75 µL, 2.16 mmol) in methylene chloride (5.0 mL) was added HBTU (152 mg, 0.396 mmol) and the reaction stirred 0.5 (2R, 3S) - 3 - Amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - 3) - 3 - Amino - 4 - (3, 5 - difluorophenyl)]15 ethylbenzyl)amino]butan-2-ol (150 mg, 0.36 mmol) was added in one portion and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, saturated sodium chloride, dried 20 sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 0-5% methanol/methylene chloride) gave  $N-\{(1S,2R)-1-(3,5$ difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino) isoquinoline-7-carboxamide (67 mg) which was 25 characterized as its bis-HCl salt: mp 262 °C dec; ESI MS m/z  $547 [M + H]^{+}$ 

### EXAMPLE SP-244

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-30 hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide

$$\begin{array}{c} \text{HATU, HOBt, DIPEA} \\ \text{NPr}_2 \\ \text{OH} \\ \\ \text{H}_2\text{N} \\ \\ \text{F} \\ \end{array} \begin{array}{c} \text{OH} \\ \text{NPr}_2 \\ \text{OH} \\ \text{F} \\ \end{array}$$

Step 1: A solution of 7-bromoisoquinolin-1-ol (2.5 g, 11.1 mmol) and POCl<sub>3</sub> (10.4 mL, 111 mmol) was stirred at 70 °C for 2.5 h. The reaction mixture was cooled to room temperature, poured into ice water, and the solution was stirred overnight. The aqueous mixture was diluted with chloroform, washed with a saturated solution of NaHCO<sub>3</sub>, saturated NaCl, dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure to afford 7-bromo-1-chloroisoquinoline (2.3 g):  $^1$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.39-8.36 (m, 2H), 8.09-8.02 (m, 2H), 7.95 (d, J = 6 Hz, 1H).

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Step 2: A solution of 7-bromo-1-chloroisoquinoline from step 1 (500 mg, 2.1 mmol) and dipropylamine (2.8 mL, 21 mmol) was heated at 150 °C in a sealed tube for 2 d. The reaction mixture was cooled, and the solvent was removed under reduced pressure to provide 7-bromo-N,N-dipropylisoquinolin-1-amine (400 mg):  $^{1}$ H NMR (300 MHz, DMSO- $d_{6}$ )  $\delta$  8.55 (s, 1H), 7.90 (d, J = 6 Hz, 1H), 7.75-7.64 (m, 2H), 6.87 (d, J = 6 Hz, 1H), 3.42 (q, J = 7 Hz, 4H), 1.65 (q, J = 7 Hz, 4H), 0.94 (t, J = 7 Hz, 6H).

Step 3: A solution of 7-bromo-N,N-dipropylisoquinolin-1-amine (350 mg, 1.1 mmol) and CuCN (204 mg, 2.2 mmol) in N,N-dimethylformamide (2 mL) was stirred at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carbonitrile (279 mg, which was used without any further characterization.

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- 1-(dipropylamino)isoquinoline-7-Α solution οf Step 4: carbonitrile from step 3 (279 mg, 1.1 mmol) in concentrated hydrochloric acid (4 mL) was heated at 150 °C in a sealed tube reaction mixture was cooled h. The to 15 for temperature, the solvent was removed under reduced pressure, dissolved in 25% and the residue was а ammonium hydroxide/water solution and stirred for 1 h. The solution was acidified to pH 4 with concentrated hydrochloric acid, and extracted with chloroform  $(3 \times 50 \text{ mL})$ . The combined organics 20 were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to provide 1-(dipropylamino)isoquinoline-7-carboxylic acid (104 mg): ESI MS m/z 273 [M + H]<sup>+</sup>.
- stirred solution ο£ 1-25 Step 5: To а (dipropylamino)isoquinoline-7-carboxylic acid (103 mg, (2R, 3S) - 3 - Amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - 4)]mmol), ethylbenzyl)amino]butan-2-ol (154 mg, 0.38 mmol), HOBt (77 mg, 0.57 mmol), and DIPEA (0.2 mL, 1.1 mmol) in methylene chloride 30 (4 mL) was added HATU (216 mg, 0.57 mmol). mixture was stirred overnight and then partitioned between methylene chloride and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and

concentrated under reduced pressure. Purification by flash column chromatography (silica, 9:1 chloroform/methanol) gave  $N-\{(1S,2R)-1-(3,5-\text{difluorobenzyl})-3-[(3-\text{ethylbenzyl})\,\text{amino}]-2-\text{hydroxypropyl}\}-1-(\text{dipropylamino})\,\text{isoquinoline-7-carboxamide}$  (70 mg): mp: 142-151 °C; APCI MS m/z 589 [M + H]<sup>+</sup>

## EXAMPLE SP-244

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1-[butyl(methyl)amino]-N- $\{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-$ 

10 ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide

Step 1: A solution of 7-bromo-1-chloroisoquinoline (750 mg, 3.09 mmol) in N-methylbutylamine (7.0 mL) was heated at 65 °C in a sealed tube for 18 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with chloroform and washed with saturated sodium bicarbonate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a brown oil. Purification by flash column chromatography (silica, 3:1 hexanes/diethyl ether) provided 7-bromo-N-butyl-N-methylisoquinolin-1-amine (730 mg): ESI MS m/z 293 [M + H]<sup>+</sup>.

25 Step 2: To a -60 °C solution of 7-bromo-N-butyl-N-methylisoquinolin-1-amine (230 mg, 0.78 mmol) in diethyl ether -615-

was added sec-butyllithium (1.00 mL of a 1.3 M solution in cyclohexanes, 1.30 mmol). The solution was stirred at -60 °C for 20 min then excess dry ice (CO2) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The aqueous phase concentrated under reduced pressure to yield a yellow oil. Purification by flash column chromatography (silica, 50:30:15:5 ethyl acetate/chloroform/methanol/ammonium 10 hydroxide) provided 1-[butyl(methyl)amino]isoquinoline-7carboxylic acid (90 mg): ESI MS m/z 259 [M + H]<sup>+</sup>.

Step 3: To a solution of 1-[butyl(methyl)amino]isoquinoline-7carboxylic acid (130 0.5 mg, mmol) and N, N-15 diisopropylethylamine (525 μL, 3.0 mmol) in methylene chloride (6.25 mL) was added HBTU (190 mg, 0.5 mmol) and the reaction mixture was stirred for 0.5 h. (2R,3S)-3-Amino-4-(3,5difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (174 0.42 mmol) was added in one portion and the reaction mixture 20 was stirred at room temperature 18 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1-5% 25 methanol in chloroform) 1-[butyl(methyl)amino]-Ngave  $\{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2$ hydroxypropyl}isoquinoline-7-carboxamide (101 mg): mp 120-121 °C; ESI MS m/z 575 [M + H]<sup>+</sup>

### 30 EXAMPLE SP-244

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[methyl(propyl)amino]isoquinoline-7-carboxamide

was prepared in a manner similar to that outlined above for  $1-[butyl(methyl)amino]-N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}isoquinoline-7-carboxamide. ESI MS <math>m/z$  561 [M + H]<sup>+</sup>

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EXAMPLE SP-245

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamide

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refluxing solution of 7-bromo-1-Step 1: To chloroisoquinoline (4.85 g, 23.28 mmol) in diethyl ether (75 mL) was added butylmagnesium chloride (17.8 mL, 2.0 M ether, 35.6 mmol) and the reaction maintained at reflux for 2 h. 15 reaction mixture was cooled to room temperature, carefully diluted with an equal volume of ethyl acetate, washed with saturated sodium bicarbonate, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an brown oil. Purification by 20 flash column chromatography (silica, 1-10% ether/hexanes) gave the desired 7-bromo-1-butylisoquinoline (1.50 g): ESI MS m/z  $264 [M + H]^{+}$ .

25 Step 2: To a -60 °C solution of 7-bromo-1-butylisoquinoline prepared in step 1 (940 mg, 3.55 mmol) in diethyl ether (15

mL) was added sec-butyl lithium (3.0 mL, 1.3 M cyclohexanes, 3.90 mmol) to yield a dark green solution. The reaction mixture was stirred at -60 °C for an additional 15 minutes at which time carbon dioxide gas was bubbled through the solution for 20 minutes with the aid of a gas dispersion tube. The allowed warm to to room solution was then resulting temperature and concentrated under reduced pressure to yield a The residue was partitioned between ethyl acetate pink solid. and water and then acidified to pH 7 with 1 N hydrochloric The aqueous phase was extracted again with ethyl acetate and the combined organic phases were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield 1-butylisoquinoline-7-carboxylic acid (299 mg). ESI MS m/z 230 [M + H]<sup>+</sup>.

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Step 3: To a solution of 1-butylisoquinoline-7-carboxylic acid (79 mg, 0.26 mmol) and N, N-diisopropylethylamine (150  $\mu$ L, 0.86 mmol) in methylene chloride (1.8 mL) was added HBTU (100 mg, 0.264 mmol) and the reaction mixture stirred for 0.5 h. of (2R,3S)-3-amino-4-(3,5-20 this added a solution difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol 0.264 mmol) in methylene chloride (1.8 mL) containing N, Ndiisopropylethylamine (150  $\mu$ L, 0.86 mmol). The reaction mixture was then stirred at room temperature overnight. reaction mixture was diluted with methylene chloride, washed 25 with saturated sodium bicarbonate, and saturated The organic layer was then dried (sodium sulfate), chloride. concentrated under reduced pressure. filtered, and Purification by flash column chromatography (silica, 93:7  $1-butyl-N-\{(1S, 2R)-1-(3, 5-$ 30 chloroform/methanol) gave difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}isoquinoline-7-carboxamide (103 mg): mp 109-110 °C; ESI MS m/z 546 [M + H]<sup>+</sup>.

EXAMPLE SP-246

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide

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1: A solution of 1-butylisoquinoline-7-carboxylic acid 1.41 mmol) methanol (25 mL) containing in (325 concentrated sulfuric acid (800 µL) was refluxed overnight. The reaction mixture was then concentrated under reduced pressure, diluted with methylene chloride, washed with water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated to yield methyl 1-butylisoquinoline-7-carboxylate (350 mg): ESI MS m/z  $244 [M + H]^{+};$ 

Step 2: To a solution of methyl 1-butylisoquinoline-7-carboxylate prepared in step 1 (350 mg, 1.44 mmol) in methanol (6.0 mL) was added platinum(IV) oxide (35 mg) and the reaction mixture stirred under one atmosphere of hydrogen at room temperature overnight. The reaction mixture was concentrated under reduced pressure and redissolved in methylene chloride (15 mL). To this solution was added di-tert-butyl dicarbonate

(350 mg, 1.6 mmol), triethylamine (500 μL, 3.11 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol), and the reaction mixture stirred at room temperature for 4 h. The reaction mixture was then diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless oil. Purification by flash column chromatography (silica, 85:15 hexanes/ethyl acetate) yielded 2-tert-butyl 7-methyl 1-butyl-3,4-dihydroisoquinoline-2,7(1H)-dicarboxylate (347 mg)l: ESI MS m/z 248 [M + H]<sup>+</sup>.

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Step 3: To a solution of 2-tert-butyl 7-methyl 1-butyl-3,4dihydroisoquinoline-2,7(1H)-dicarboxylate prepared in step 2 (347 mg, 1.0 mmol) in 2:1:1 dioxane/methanol/water (6.6 mL) 15 was added lithium hydroxide monohydrate (125 mg, 3.0 mmol) and the reaction mixture stirred 24 h at room temperature. reaction mixture was concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N hydrochloric acid to 20 pH 1 and extracted several times with 3:1 chloroform/2-The combined organic phases were washed with water propanol. (sodium saturated sodium chloride, dried sulfate), filtered, and concentrated under reduced pressure to provide 25 2-(tert-butoxycarbonyl)-1-butyl-1,2,3,4tetrahydroisoquinoline-7-carboxylic acid (205 mg). ESI MS m/z $332 [M - H]^{-}$ .

Step 4: To a solution of 2-(tert-butoxycarbonyl)-1-butyl-30 1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid (205 mg, 0.61 mmol) and N,N-diisopropylethylamine (150 µL, 0.86 mmol) in methylene chloride (4.0 mL) was added HBTU (233 mg, 0.61 mmol) and the reaction mixture stirred for 0.5 h. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-

ethylbenzyl)amino]butan-2-ol (250 mg, 0.61 mmol) in methylene chloride (4.0 mL) containing N, N-diisopropylethylamine (150  $\mu$ L, The reaction mixture was then stirred at room 0.86 mmol). temperature overnight. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, 5 and saturated sodium · chloride. The organic layer was then (sodium sulfate), filtered, and concentrated under Purification by flash column chromatography reduced pressure. (silica, 95:5 chloroform/methanol) gave the desired amide The amide was then dissolved in dioxane (5.0 mL) to 10 product. which was added hydrochloric acid (20 mL, 4.0 M dioxanes, 80 mmol) and the reaction mixture stirred overnight. reaction mixture was then concentrated to dryness and purified flash column chromatography (silica, 90:6:3:1 15 acetate/chloroform/methanol/ammonium hydroxide) to yield a colorless oil. The oil was partitioned between chloroform/2-propanol, washed with water, and saturated sodium The organic layer was then dried (sodium sulfate), chloride. filtered, and concentrated to yield a white solid. The solid 20 was dried under high vacuum at 45  $^{\circ}\text{C}$  in the presence of P2O5 to  $1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-difluorobenzyl)]}$ ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4tetrahydroisoquinoline-7-carboxamide(140 mg) characterized as a mixture of diastereomers: mp 121-124 °C; ESI MS m/z 550 [M + 25 H]\*.

#### EXAMPLE SP-247

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N-{(1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride

PCT/US02/36072 WO 03/040096

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Step 1: Di-tert-butyl-dicarbonate (10.8 g, 49 mmol) was added to an ice-cold solution of R-pyrrolidinemethanol (5.0 g, 49 mmol) and triethylamine (7.6 mL, 55 mmol) in 125 mL of  $CH_2Cl_2$ . The resultant solution was warmed to ambient temperature and solution overnight. The reaction stirred concentrated, diluted with EtOAc, washed 2X with 1 M KH2PO4 and 2X with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to (2R)-2-(hydroxymethyl)pyrrolidine-1tert-butyl afford carboxylate (9.9 g).

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Oxalyl chloride (9.0 mL, 100 mmol) was added to a solution of DMSO (10.5 mL, 150 mmol) in 80 mL of  $CH_2Cl_2$  at -78 °C, under a nitrogen atmosphere. The solution was stirred for 20 min at -78 °C, tert-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.9 g, 49 mmol) was added, and the resultant solution stirred at -78 °C for 20 min. Triethylamine (28 mL, 200 mmol) was added to the reaction solution, the dry iceacetone bath was removed, and the resultant solution was allowed to stir for two hours, slowly warming to ambient The reaction solution was quenched with brine, temperature. the phases were separated, and the organic phase was washed with 1 M KH2PO4 and saturated NaHCO3. The organic solution was then dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to an orange 25 This oil was then dissolved in heptane, filtered through oil.

a plug of silica gel eluting with heptane, and the filtrate was concentrated to yield tert-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.87 g).

Step 3: n-Butyl lithium (1.6 M in hexanes) (27 mL, 43 mmol) 5 was added to ice-cold hexamethyldisilazane (9.2 mL, 44 mmol) The solution was stirred for 10 under a nitrogen atmosphere. added to а suspension then min and was methyl(triphenylphosphonium)bromide (15.5 g, 43 mmol) in 100 mL of THF at ambient temperature. After stirring for 1 h, the 10 mixture was cooled to -78 °C and a solution of tert-butyl (2R)-2-formylpyrrolidine-1-carboxylate (7.9 g, 40 mmol) in 50 mL of The cold bath was removed and the mixture THF was added. stirred overnight at ambient temperature. The reaction mixture was then quenched with saturated NH4Cl, the phases were 15 separated, and the organic phase was washed with saturated NH4Cl, brine, dried over Na2SO4, filtered, and concentrated to give an orange oil. The oil was purified on a Biotage 40M column eluting with heptane to give tert-butyl (2R)-2vinylpyrrolidine-1-carboxylate (5.0 g). 20

Step 4: To a suspension of palladium (II) hydroxide on activated carbon (20% by wt, 1.2 g) in 10 mL of ethanol was added tert-butyl (2R)-2-vinylpyrrolidine-1-carboxylate (2.0 g, 10 mmol)as a solution in 15 mL of ethanol and the mixture was placed under 12 psi of  $H_2$  on a parr hydrogenator overnight. The resultant mixture was then filtered and concentrated to give tert-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.5 g).

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Step 5: To a solution of tert-butyl (2S)-2-ethylpyrrolidine-1-carboxylate (1.0 g, 5.0 mmol) in 10 mL of dioxane was added 8 mL of 6N HCl and the resultant solution stirred overnight at ambient temperature. The reaction solution was then

concentrated, turned basic with solid KOH, and extracted with EtOAc. The combined organic extracts were dried over  $Na_2SO_4$ , filtered and concentrated to give (2S)-2-ethylpyrrolidine hydrochloride (0.30 g).

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Step 6: A solution of 3-(methoxycarbonyl)-5-methylbenzoic acid (0.48 g, 2.5 mmol), HATU (1.0 g, 2.6 mmol), and HOAt (0.37 g, 2.7 mmol) in 10 mL of dry DMF was stirred for an hour over ice, under a nitrogen atmosphere prior to the of (2R, 3S) - 3 - amino - 4 - (3, 5 - diffuorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3, 5 - diffuorophenyl)]] - 1 - [(3 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - (3 - amino - 4 - amino - 4 - amino - 4 - (3 - amino - 4 - aaddition ethylbenzyl)amino]butan-2-ol dihydrochloride (1.0 g, 2.5 mmol) and DIPEA (1.8 mL, 10 mmol). The solution was stirred overnight at ambient temperature. The reaction solution was then quenched with 1 M HCl, diluted with EtOAc, and the phases were separated. The organic phase was washed with 1 M HCl, the combined acid washings were back-extracted with EtOAc, and the organic phases combined. The combined organic phases were then washed with saturated NaHCO3, brine and dried over Na2SO4 The mixture was filtered and concentrated to give the coupled product as an orange oil. This oil was dissolved in 35 mL of MeOH and solid LiOHH2O (0.6 g, 14 mmol) was added with 2 mL of water. The mixture was stirred overnight at ambient

The solution was concentrated, diluted with temperature. water, neutralized with 1 M HCl, and concentrated. resulting oily residue was purified on a Biotage 40S column eluting with 5% MeOH in CH2Cl2 to give a colorless oil. This was dissolved in 10 mL of MeOH and 3 mL of 1 M HCl in ether was added. The solution was concentrated and the residue with heptane to give  $3-[({(1S,2R)-1-(3,5-)}$ triturated difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

hydroxypropyl amino carbonyl]-5-methylbenzoic

acid

hydrochloride (0.65 g). 10

To a solution of  $3-[({(1S,2R)-1-(3,5-difluorobenzyl)-}$ 3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-5methylbenzoic acid hydrochloride (0.50 g, 0.94 mmol) and ditert-butyldicarbonate (0.20 g, 0.92 mmol) in 10 mL of methanol 15 and 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was added triethylamine (0.40 mL, 2.9 The solution was stirred for 2.5 hours at ambient mmol). temperature, at which time it was concentrated, partitioned between EtOAc and 1 M  $KH_2PO_4$ , and the phases were separated. The organic phase was washed with M KH<sub>2</sub>PO<sub>4</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, 20 filtered, concentrated, and triturated with heptane to give 3-({[(1S,2R)-3-[(tert-butoxycarbonyl)(3-ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]amino}carbonyl)-5methylbenzoic acid (0.50 g).

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Step 8: A solution of 3-({[(1S,2R)-3-[(tert-butoxycarbonyl)(3ethylbenzyl)amino]-1-(3,5-difluorobenzyl)-2hydroxypropyl]amino}carbonyl)-5-methylbenzoic acid 0.50 mmol), HATU (0.19 g, 0.50 mmol) and HOAt (0.07 g, 0.51 30 mmol) in 5 mL of dry DMF under a nitrogen atmosphere was stirred for 15 minutes. A solution of (2S)-2-ethylpyrrolidine hydrochloride (0.05 g, 0.50 mmol) and DIPEA (0.35 mL, 2.0 mmol) in 5 mL of DMF was added. The solution was stirred overnight at ambient temperature. It was then quenched with 1

M HCl, diluted with EtOAc, and the phases were separated. organic phase was washed with 1 M HCl, saturated NaHCO3, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give an orange-brown This oil was purified on a Biotage 40S column eluting oil. with 200 mL of CH<sub>2</sub>Cl<sub>2</sub>, then 3% MeOH in CH<sub>2</sub>Cl<sub>2</sub>. The yellow oil obtained was dissolved in 4 mL of CH2Cl2 and 4 mL of TFA was After stirring for two hours at ambient temperature added. the reaction solution was concentrated and the residue was purified by reverse phase prep hplc using a 1-inch Kromasil c18 column to give the product as the formic acid salt. 10 was then converted to the HCl salt by the addition of 2 mL of 1 M HCl in ether. Upon concentration and trituration with  $N-\{(1S, 2R)-1-(3, 5-difluorobenzy1)-3-[(3-max)]$ heptane ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-

15 ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride was obtained (0.010 g). MS m/z 579.0 [M + H].

## EXAMPLE SP-248

The following compounds,

3-{[(2S)-2-butylpyrrolidin-1-yl]carbonyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-

hydroxypropyl}-5-methylbenzamide, MS m/z 606.4 [M + H];

 $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-difluorobenzyl)]$ 

ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-{[(2S)-2-

25 propylpyrrolidin-1-yl]carbonyl}benzamide formic acid salt, MS
 m/z 638.6 [M + H];

 $N-\{(1S, 2R)-1-(3, 5-difluorobenzy1)-3-[(3-4)]$ 

ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(2-

methoxyethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide, MS

30 m/z 608.6[M + H]; and

 $N-\{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-1)]$ 

ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-

ethylpyrrolidin-1-yl]carbonyl}-5-methylbenzamide

hydrochloride; were prepared in a manner similar to that outlined above for EXAMPLE SP-247.

### EXAMPLE SP-249

5 The following compounds;

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS m/z 608.3 [M + H];

N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS m/z 590.3 [M + H]; and

15 N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamide hydrochloride, MS m/z 620.3 [M + H]; were also prepared using the methods disclosed herein.

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EXAMPLE SP-250

Preparation of: N-[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide:

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Step 1: A stirred solution of N- $\{(1S)-2-(3,5-\text{difluorophenyl})-1-[(2S)-\text{oxiran}-2-\text{yl}]$  ethyl $\}$  acetamide (4.96 g) and 1-(3-bromophenyl) cyclopropylamine (8.6 g) in 60 mL of i-PrOH was heated to 75 °C for 3 h. The cooled solution was evaporated and the residue re-dissolved in ethyl acetate (200 mL). The organic layer was washed with 10 % aqueous HCl (25 mL x 2). The aqueous washings were extracted once with EtOAc (75 mL) and the combined organic layers washed with a saturated solution of NaCl (100 mL). The organic layers were then dried

over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield a residue that was purified by column chromatography to give 5.0 g of tert-butyl (1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropylcarbamate.

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To a suspension of tert-butyl  $(1S, 2R)-3-\{[1-(3-1)]$ Step 2: bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2hydroxypropylcarbamate (1.3 g) in 5.0 mL of dichloromethane was added 5.0 mL of trifluoroacetic acid at 23 °C. stirring for 1 h, 10.0 mL of toluene was added and the 10 The resulting residue was re-dissolved solution evaporated. in toluene and the solution evaporated. This procedure was After drying under high vacuum for 2 h, repeated once more. the residue was suspended in dichloromethane (10.0 mL) and triethylamine (0.5 g) and acetylimidazole (0.3 g) were added. 15 The solution was stirred for 4 h and concentrated under The residue was purified by column reduced pressure. chromatography to yield 0.90 g of the title compound. ES+ found  $(M+H^+)$ : 455.

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### EXAMPLE SP-251

Preparation of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide:

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solution οf  $N-[(1S, 2R)-3-\{[1-(3-$ To a bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2hydroxypropyl]acetamide (0.030 g) in DMF (0.75 mL) was added 3-methoxyphenylboronic acid (0.030 g), Cs<sub>2</sub>CO<sub>3</sub> (0.085 g) and The mixture was heated for 12 h at 90 °C. The  $Pd(Ph_3P)_4$ . cooled solution was diluted with EtOAc (15 mL) and washed with brine  $(10 \text{ mL } \times 2)$ . The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. filtered, The

resulting residue was purified by column chromatography to give 0.010 g of the title compound. ES+ found  $(M+H^{+})$ : 481.

# EXAMPLE SP-251

- 5 N-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({1-[3'-(hydroxymethyl)-1,1'-biphenyl-3-yl]cyclopropyl}amino)propyl]acetamide, was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-
- 10 yl)cyclopropyl]amino}propyl)acetamide step 1, using 3- (hydroxymethyl)phenylboronic acid (0.036 g) to give 0.008 g of the title compound. ES+ found (M+H<sup>+</sup>):481.

### EXAMPLE SP-252A

N-[(1S,2R)-3-{[1-(2'-acetyl-1,1'-biphenyl-3-yl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]acetamide was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide step 1, using 2-acetylphenylboronic acid (0.032 g) to give 0.012 g of the title compound. ES+ found (M+H<sup>+</sup>): 493.

# EXAMPLE SP-252B

yl)phenyl]cyclopropyl}amino)-2-hydroxypropyl]acetamide was prepared by the method of N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[1-(3'-methoxy-1,1'-biphenyl-3-yl)cyclopropyl]amino}propyl)acetamide step 1, using 5-formylthien-2-ylboronic acid (0.030 g) to give 0.005 g of the title compound. ES+ found (M+H<sup>+</sup>):484.

# EXAMPLES 2453A to 2453D

# EXAMPLE SP-253A

N<sup>1</sup>-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide hydrochloride;

5 EXAMPLE SP-253B

 $N^{1}$ -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl- $N^{3}$ ,  $N^{3}$ -dipropylisophthalamide hydrochloride;

10 EXAMPLE SP-253C

 $N^{1}-\{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-5-methyl-N^{3},N^{3}-dipropylisophthalamide hydrochloride;$ 

15 EXAMPLE SP-253D

 $N^{1}$ -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl- $N^{3}$ ,  $N^{3}$ -dipropylisophthalamide hydrochloride;

20 EXAMPLE SP-254A

 $N^{1}$ -{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- $N^{3}$ ,  $N^{3}$ -dipropylisophthalamide hydrochloride (EXAMPLE SP-254) and  $N^{1}$ -[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl- $N^{3}$ ,  $N^{3}$ -dipropylisophthalamide hydrochloride (EXAMPLE Si 255)

Step 1: Cyclopentyl magnesium bromide (8 mL of 2M ethereal solution) was added to cuprous bromide/dimethylsulfide complex (0.33 g, 1.6 mmol) in 10 mL of dry THF cooled to - 25°C under nitrogen. After 20 min, a solution of tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1-carboxylate (1.95 g, 8 mmol) in 4 mL of dry THF was introduced. The mixture was allowed to warm to ambient temperature overnight. It was quenched with saturated aqueous NH<sub>4</sub>Cl and extracted with ethyl ether. The organic phase was washed with aqueous saturated NH<sub>4</sub>Cl, 1 N NaHCO<sub>3</sub>, and brine. It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated to 2.38 g of a solid. This material was dissolved in 70 mL of methanol, 12 g of Dowex 50WX2-400 was

added, and the mixture was refluxed for 2 h. The mixture was filtered, washing with methanol and dichloromethane. A clean receiver was attached, and the resin was washed with 100 mL of 1:1 concentrated NH4OH: ethanol. The filtrate was concentrated to 1.16 g of tan crystals. The crystals were dissolved in 30 mL of dry THF, and 1.5 g (6.9 mmol) of di-t-butyldicarbonate introduced. The mixture was stirred under nitrogen overnight. It was concentrated, extracted with ether and the ether was washed with several portions of water and brine. Drying over Na<sub>2</sub>SO<sub>4</sub> and concentration afforded 1.8 g (6.7 mmol, 10 84% from tert-butyl (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4yl]aziridine-1-carboxylate) of tert-butyl [cyclopentylmethy]-2,3-dihydroxypropylcarbamate: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.5 (d, 1 H, NH), 3.7 (m, 1 H), 3.6-3.49 (m, 2 H), 3.36 (m, 1 H), 3.26 (t, 1 H, OH), 2.76 (d, 1 H, OH), 1.45 (s, 9 H), 1.88-15 1.36 (m, 9 H), 1.17-1.08 (m, 2 H).

Step 2: Toluenesulfonyl imidazole (Ts-Im, 2.22 g, 10 mmol) was tert-butyl (1S,2S)-1-[cyclopentylmethy]-2,3added 20 dihydroxypropylcarbamate (1.8 g, 6.7 mmol) in 15 mL of dry THF under nitrogen, cooled in an ice bath. To this was added 13.4 mL (13.4 mmol) of a 1M solution of potassium-t-butoxide in THF over 8 min. After 5 min, the ice bath was removed and the orange mixture was stirred for 3 h. It was quenched with 1 N  $\ensuremath{\mbox{KH}_2\mbox{PO}_4}$  and diluted with ether. The organic phase was washed 25 with 1 N KH2PO4, water, and brine. The solution was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and chromatographed over silica gel, eluting with 5% dichloromethane, 15% ethyl acetate, and 80% heptane. Fraction 4 afforded 900 mg of a 2:1 mixture of tert-(1S) -2-(cyclopentyl) -1-[(2S)-oxiran-2-yl]ethylcarbamate 30 and a side product. Fraction 5 afforded 230 mg of tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate: <sup>1</sup>H NMR  $(CDCl_3)$   $\delta$  4.56 (d, 1 H), 3.45 (m, 1 H), 2.85 (m, 1 H), 2.75 (m,

2 H), 1.91 (m, 1 H), 1.8 (m, 2 H), 1.6-1.4 (m, 6 H), 1.44 (s, 9 H), 1.13-1.07 (m, 2 H).

### EXAMPLE SP-254B

N<sup>1</sup>-{(1S,2R)-1-(cyclopentylmethyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}-5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide hydrochloride

Step 3: To tert-butyl (1S)-2-(cyclopentyl)-1-[(2S)-oxiran-2yl]ethylcarbamate (230 mg, 0.9 mmol) was added 260 mg (1.9 10 mmol) of m-ethylbenzylamine in 5 mL of isopropanol. mixture was refluxed for 1.5 h under nitrogen, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% 15 HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined organic phases were washed with 1 N NaHCO3 and brine, dried over Na2SO4, and concentrated. The residue was partially purified by forming the HCl salt, triturating with pentane, and then neutralizing to the free 20 base (290 mg, 0.74 mmol). To this was added 2 mL of trifluoroacetic acid (TFA) and 2 mL of dichloromethane, the mixture was stirred under nitrogen for 30 min. It was concentrated to an oil which was dissolved in 2 mL of dry THF and neutralized with 0.2 mL of 4-methyl morpholine. To this 25 mixture was added a solution of 3-[(dipropylamino)carbonyl]-5methylbenzoic acid (0.2 g, 0.76 mmol) and carbonyldiimidazole (CDI, 0.13 g, 0.8 mmol) in 3 mL of dry THF, which had been stirring together for 35 min. The reaction was stirred under nitrogen overnight. To the mixture was added 1 N KH2PO4 and ethyl acetate. The organic phase was washed with 1 N KH2PO4, 1 30 N NaHCO3 (2X) and brine, dried over Na2SO4, and concentrated. Chromatography over silica gel, eluting with 6% methanol (containing 1% NH4OH) in dichloromethane afforded 109 mg (0.19 mmol)  $N^{1}$ -{(1S, 2R)-1-(cyclopentylmethyl)-3-[(3of

ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl- $N^3$ , $N^3$ -dipropylisophthalamide hydrochloride (EXAMPLE SP-254) after formation of the salt with ethereal HCl: CI MS m/z 536 [M+H]<sup>+</sup>.

- 5 EXAMPLE SP-255  $N^{1}-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-hydroxypropyl]-5-methyl-N^{3}, N^{3}-dipropylisophthalamide hydrochloride$
- fraction containing tert-butyl (1S)-2-10 Step The (cyclopentyl)-1-[(2S)-oxiran-2-yl]ethylcarbamate (ca. 2 mmol) and a side product, described in the above example, reacted with m-bromobenzylamine (10 mmol) in12 mL οf isopropanol at reflux for 3 h. The solvent was removed and the residue was dissolved in ethyl acetate. This was washed with 15 several portions of 10% HCl, 1 N NaHCO3, and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated. Chromatography on silica gel, eluting with dichloromethane, then up to 2% of methanol (containing 1% NH4OH) in dichloromethane afforded 523 mg ( 1.19 mmol, 60% based on epoxide) of the oily addition product. This material 20 (0.31 g, 0.7 mmol) was dissolved in 2 mL of dichloromethane, and 1 mL of TFA was added. After 1 h it was concentrated, dissolved in ethyl acetate, neutralized with 1 N NaHCO3, washed with brine, and concentrated to the free base. To this was added 4 mL of dry THF and a pre-mixed (for 2 h) solution of 3-25 [(dipropylamino)carbonyl]-5-methylbenzoic acid (190 mg, 0.72 mmol) and CDI (120 mg, 0.74 mmol) in 3 mL of dry THF. After 2 days the reaction was quenched with 1 N KH2PO4 and dissolved in ethyl acetate.
- 30 The organic phase was washed with 1 N KH<sub>2</sub>PO<sub>4</sub>, 1 N NaHCO<sub>3</sub> (2X) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Chromatography over silica gel, eluting with 5% methanol (containing 1% NH<sub>4</sub>OH) in dichloromethane afforded 184 mg (0.29 mmol) of N<sup>1</sup>-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclopentylmethyl)-2-

hydroxypropyl]-5-methyl- $N^3$ ,  $N^3$ -dipropylisophthalamide hydrochloride EXAMPLE SP-255 as a white solid after formation of the salt with ethereal HCl: CI MS m/z 586  $[M+H]^+$ .

- 5 N<sup>1</sup>-{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide hydrochloride (EXAMPLE SP-256) and N<sup>1</sup>-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide hydrochloride (EXAMPLE SP-257)
- Step 1: Cyclohexyl magnesium bromide was prepared by adding cyclohexyl bromide (2.46 mL, 20 mmol) to magnesium turnings (0.97 g, 40 mmol) in dry THF (20 mL) and refluxing for 1.5 h. Following the procedures described in step 1 for the previous (1S, 2S) -1 - [cyclohexylmethy] -2,3-S-tert-butyl EXAMPLE dihydroxypropylcarbamate was obtained as 1.66 g (5.8 mmol, 70% (2R)-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4from tert-butyl yl]aziridine-1-carboxylate) of a slightly yellow oil which solidified on standing:  $^{1}\text{H}$  NMR (CDCl3)  $\delta$  4.43 (d, 1 H, NH), 20 3.69 (m, 1 H), 3.59 (m, 2 H), 3.32 (m, 1 H), 3.24 (t, 1 H, OH), 2.70 (d, 1 H, OH), 1.45 (s, 9 H), 1.8-1.13 (m, 11 1.01 (m, 1 H), 0.87 (m, 1 H).
- 25 Step 2: tert-Butyl (1S,2S)-1-[cyclohexylmethy]-2,3dihydroxypropylcarbamate (1.6 g, 5.5 mmol) was reacted with
  Ts-Im (1.5 g, 6.75 mmol) and potassium t-butoxide (11 mL of a
  1 M solution in THF) in 20 mL of dry THF according to the
  procedure described in step 2 for the preceding example.
  30 Chromatography on silica gel, eluting with 5% dichloromethane
  and 5%, increasing to 15% ethyl acetate in heptane afforded
  456 mg 1.7 mmol, of tert-butyl (1S)-2-(cyclohexyl)-1-[(2S)oxiran-2-yl]ethylcarbamate: ¹H NMR (CDCl<sub>3</sub>) δ 4.41 (m, 1 H),

3.55 (m, 1 H), 2.84 (m, 1 H), 2.75 (m, 2 H), 1.8-1.6 (m, 4 H), 1.45 (s, 9 H), 1.4-1.1 (m, 7 H), 0.98 (m, 1 H), 0.86 (m, 1H).

### EXAMPLE SP-256

 $N^{1}-\{(1S,2R)-1-(cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-5-methyl-N^{3},N^{3}-dipropylisophthalamide hydrochloride$ 

tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-3: Step yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with methyl benzylamine (254 mg, 1.9 mmol) in 5 mL of isopropanol under nitrogen for 1.5 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined 15 organic phases were washed with 1 N NaHCO3 and brine, dried over  $Na_2SO_4$ , and concentrated. The resulting oil (300 mg) was dissolved in 2 mL of dichloromethane and 2 mL of TFA and stirred for 30 min. It was concentrated, and by weight determined to contain 4 eq. of TFA. This was dissolved in 2 mL 20 of dry THF, and 0.4 mL (3.6 mmol) of 4-methyl morpholine was added. This was cooled to - 30°C, and a mixture of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (238 mg, mmol) and CDI (165 mg, 1 mmol) in 3 mL of dry THF, which had previously been stirred together for 1 h at room temperature, 25 The mixture was allowed to warm to ambient was added. temperature. After 3 days the reaction was quenched with 1 N  $\mathrm{KH_{2}PO_{4}}$  and dissolved in ethyl acetate. The organic phase was washed with 1 N KH2PO4, 1 N NaHCO3 (2X) and brine, dried over and concentrated. Chromatography over silica gel, 30  $Na_2SO_4$ , eluting with 4% to 10% methanol (containing 1% NH4OH) in dichloromethane afforded 124 mg (0.21 mmol) of  $N^1-\{(1S,2R)-1-(1S,2R)\}$ (cyclohexylmethyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $5-methyl-N^3, N^3-dipropylisophthalamide$  hydrochloride

SP-256) as a white solid after formation of the salt with ethereal HCl: CI MS m/z 550 [M+H]<sup>+</sup>.

EXAMPLE SP-257

N<sup>1</sup>-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(cyclohexylmethyl)-2hydroxypropyl]-5-methyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide hydrochloride

tert-Butyl (1S)-2-(cyclohexyl)-1-[(2S)-oxiran-2-3: Step yl]ethylcarbamate (225 mg, 0.84 mmol) was refluxed with m-10 bromobenzylamine (380 mg, 2.0 mmol) in 7 mL of isopropanol under nitrogen for 2 h, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. It was washed three times with small portions of 10% HCl, and the aqueous phases were back-extracted with ethyl acetate. The combined 15 organic phases were washed with 1 N NaHCO3 and brine, dried over  $Na_2SO_4$ , and concentrated. The resulting oil (356 mg) was dissolved in 3 mL of dichloromethane and 2 mL of TFA and stirred for 1.5 h. It was concentrated, and by weight determined to contain 3 eq. of TFA. To this was added 2 mL of 20 dry dimethylformamide (DMF) and 0.35 mL (3.2 mmol) of 4-methyl morpholine. To this was added a pre-mixed solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (240 mg, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide mmol), and 1hydrochloride (EDC, 190 mg, mmol), 25 hydroxybenzotriazole hydrate (HOBT, 135 mg, 1 mmol) in 3 mL of dry DMF, which had been stirring together for 1.5 h. . After 3 days the reaction was quenched with 1 N KH2PO4 and dissolved in ethyl acetate. The organic phase was washed with 1 N KH2PO4, 1 N NaHCO3 (2X) and brine, dried over Na2SO4, and concentrated. 30 Chromatography over silica gel, eluting with 5% methanol (containing 1%  $NH_4OH$ ) in dichloromethane afforded 208 mg (0.32  $N^{1}$ -[(1S, 2R)-3-[(3-bromobenzyl)amino]-1mmol) οf (cyclohexylmethyl)-2-hydroxypropyl]-5-methyl-N<sup>3</sup>, N<sup>3</sup>-

dipropylisophthalamide hydrochloride (EXAMPLE SP-257) after formation of the salt with ethereal HCl: CI MS m/z 600 [M+H}<sup>+</sup>.

EXAMPLE SP-258

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Step 1: Trimethyloxonium tetrafluoroborate (2.46 g, 16.7 mmol) was added dropwise at room temperature to a solution of 4-cyanopyridine N-oxide (compound 35, above) (2.0 g, 16.7 mmol) in methylene chloride (260 mL) and the reaction mixture stirred at room temperature overnight. The reaction was concentrated under reduced pressure to give the desired 4-cyanopyridinum N-methoxy tetrafluoroborate: <sup>1</sup>H NMR (300 MHz,

DMSO- $d_6$ )  $\delta$  9.80 (d, J = 6.0 Hz, 2H), 8.87 (d, J = 6.0 Hz, 2H), 4.48 (s, 3H).

Step 2: An aqueous solution of ammonium persulfate (8.3 mL, 8.3 mmol) was added to a refluxing solution of the Nmethoxypyridinium salt prepared in step 1 was dissolved in methanol (200 mL). After stirring for 0.5 h, additional 1 M ammonium persulfate was added (4.2 mL, 4.2 mmol) and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and concentrated under 10 reduced pressure. The residue was partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. 15 Purification by flash column chromatography (silica, 98:2 methylene chloride/methanol) gave 4-cyano-2hydroxymethylpyridine (36) as a white solid (670 mg, 30%): 1H NMR (300 MHz, CDCl3)  $\delta$  8.75 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 0.5 Hz, 1H), 7.46 (dd, J = 5.3, 0.5 Hz, 1H), 4.85 (d, J = 5.3)20 Hz, 2H), 3.25 (t, J = 5.3 Hz, 1H).

Step 3: Bromine (1.07 mL, 20.8 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (5.53 g, 21.1 mmol) in methylene chloride (97 mL). The solution was warmed to room temperature and a white precipitate was observed. 4-Cyano-2hydroxymethylpyridine 36 (2.61 g, 19.5 mmol) in methylene chloride (20 mL) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash (silica, 99:1 methylene chromatography Column

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chloride/methanol) gave 4-cyano-2-bromomethylpyridine (3.95 g), which was used immediately in the next step without further purification:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.76 (d, J = 5.0 Hz, 1H), 7.7 (s, 1H), 7.46 (dd, J = 5.0, 1.3 Hz, 1H), 4.58 (s, 2H).

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Step 4: Dimethylamine hydrochloride (4.78 g, 58.6 mmol) was added to a solution of 4-cyano-2-bromomethylpyridine (3.95 g, 19.5 mmol) and triethylamine (13.58 mL, 97.7 mmol) in acetone (40 mL). The reaction mixture was stirred overnight at room 10 temperature in a sealed tube. The reaction mixture was concentrated under reduced pressure and partitioned between methylene chloride and saturated sodium bicarbonate. organic layer was separated and washed with water, saturated sodium chloride, dried (sodium sulfate), filtered, and 15 concentrated under reduced pressure. Purification by flash 99:1 chromatography (silica, methylene column desired 4-cyano-2chloride/methanol) gave the (dimethylamino) methylpyridine (2.10 g): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.73 (d, J = 5.0 Hz, 1H), 7.71 (s, 1H), 7.41 (dd, J = 5.0, 20 1.2 Hz, 1H), 3.65 (s, 2H), 2.31 (s, 6H); ESI MS m/z 162 [M + H]<sup>+</sup>.

Step 5: A mixture of 4-cyano-2-(dimethylamino)methylpyridine (800 mg, 4.97 mmol), palladium (80 mg, 10% Pd/C) 25 concentrated hydrochloric acid (3 mL) in methanol (30 mL) was shaken under 60 psi of hydrogen overnight. The reaction mixture was filtered through diatomaceous earth and the filter cake rinsed with water and methanol. The filtrate was and the residue 30 concentrated under reduced pressure partitioned between water and methylene chloride. The aqueous layer was made alkaline with 1 N sodium hydroxide and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate),

filtered, and concentrated under reduced pressure to give an orange oil. Purification by flash column chromatography (97:3 2-propanol/ammonium hydroxide) gave 4-aminomethyl-2-(dimethylamino) methylpyridine 37 (492 mg):  $^{1}$ H NMR (500 Hz, CDCl<sub>3</sub>)  $\delta$  8.50 (d, J = 5.1 Hz, 1H), 7.37 (s, 1H), 7.15 (d, J = 5.1 Hz, 1H), 3.91 (s, 2H), 3.58 (s, 2H), 2.30 (s, 6H); ESI MS m/z 166 [M + H] $^{+}$ .

A mixture of 4-aminomethyl-2-(dimethylamino) Step 6: methylpyridine 37 (490 mg, 2.98 mmol) and tert-butyl (1S)-2-10 (3;5-difluorophenyl)-1-[(2S)-oxiran-2-yl] ethylcarbamate mg, 2.98 mmol) in 2-propanol (20 mL) was heated at reflux The reaction mixture was cooled to room overnight. temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (99:1 2-15 propanol/ammonium hydroxide) to give product (590 mg): ESI MS m/z 465 [M + H]<sup>+</sup>.

Step 7: Hydrogen chloride (6.3 mL of a 4 N solution in dioxane, 25 mmol) was added at room temperature to a solution of the yellow solid prepared in step 6 (590 mg, 1.26 mmol) in dioxane (6.3 mL) and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in methylene chloride containing N,N-diisopropylethylamine (3 mL). The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the product (523 mg): ESI MS m/z 365 [M + H]<sup>+</sup>

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Step 8: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **38** (120 mg, 0.38 mmol) in methylene chloride (3.8 mL) containing *N,N*-diisopropylethylamine (132 µL, 0.76 mmol) and HBTU (151 mg, 0.40 mmol) was stirred at

room temperature for 0.5 h. To the above solution was added a solution of the orange oil from step 7 (207 mg, 0.57 mmol) in containing N, Nchloride (3.8 mL) methylene diisopropylethylamine (132  $\mu L$ , 0.76 mmol) and the reaction mixture was stirred at room temperature for 18 h. reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an oily Purification by flash column chromatography (silica, 10 90:10 methylene chloride/methanol) gave  $N^1-\{(1S,2R)-1-(3,5-1)\}$ methyl]pyridin-4difluorobenzyl)-3-[({2-(dimethylamino) ylmethyl)amino]-2-hydroxypropyl -5-(1,3-oxazol-2-yl)-N<sup>3</sup>,N<sup>3</sup>dipropylisophthalamide (178 mg): mp 63-66 °C; ESI MS m/z 663  $[M + H]^{\dagger}$ . 15

#### EXAMPLE SP-259

Synthesis of 2-cyano-4-(dimethylamino)methylpyridine (92)

Step 1: A mixture of 4-(hydroxymethyl)pyridine (17.4 g, 159 5 mmol), t-butyldimethylsilyl chloride (26.36 g, 174.88 mmol), and imidazole (13.31 g, 195.5 mmol) in N,N-dimethyformamide (200 mL) and methylene chloride (20 mL) was stirred overnight The reaction mixture was concentrated at room temperature. under reduced pressure and then partitioned between water and 10 a mixture of ethyl acetate and hexanes (1:1). The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (35.62 g):  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.43 (d, J = 6 Hz, 2H), 7.13 (d, J = 6 Hz, 2H), 4.63 (s, 2H), 0.84 (s, 9H), 15 0.05 (s, 6H).

Step 2: To a stirred solution of the oil from step 1 (35.62 g, 159 mmol) in dry methylene chloride (470 mL) was added 3-

choloroperoxybenzoic acid (47.03 g, 172.57 mmol). The reaction mixture was stirred at room temperature overnight and then partitioned between water and methylene chloride. The organic layer was washed with saturated sodium sulfite, saturated sodium bicarbonate, 1 N sodium hydroxide, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 4-(t-butyldimethylsilyloxy)methylpyridine N-oxide 91 (37.8 g):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.07 (d, J = 6 Hz, 2H), 7.13 (d, J = 6 Hz, 2H), 4.59 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

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Step 3: A mixture of 4-(t-butyldimethylsilyloxy)methylpyridine N-oxide 91 (30 g, 125 mmol), triethylamine (40 mL), and trimethylsilylcyanide (44 mL, 360 mmol) was refluxed overnight. The black solution was cooled to room temperature and concentrated under reduced pressure to give a black gum. Purification by flash column chromatography (silica, 10:90 ethyl acetate/hexanes) gave an oil (20.3 g):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.50 (d, J = 5 Hz, 1H), 7.55 (s, 1H), 7.34 (d, J = 5 Hz, 1H), 4.66 (s, 2H), 0.83 (s, 9H), 0.05 (s, 6H).

Step 4: Bromine (1.97 mL, 38.74 mmol) was added slowly at 0 °C to a solution of triphenylphosphine (10.29 g, 39.28 mmol) in methylene chloride (200 mL). The solution was warmed to room temperature and a white precipitate was observed. The brown oil from step 3 (9.0 g, 36.27 mmol) in methylene chloride (50 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown solid. Purification by flash column chromatography (silica, 17:83 ethyl acetate/hexanes) gave a white solid (6.20

g):  ${}^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.71 (d, J = 3 Hz, 1H), 7.73 (s, 1H), 7.55 (dd, J = 6, 3 Hz, 1H), 4.42 (s, 2H).

Step 5: To a stirred solution of the solid from step 4 (9.1 g, 46.44 mmol) in acetone (90 mL) was added dimethylamine hydrochloride (11.36 g, 139.3 mmol) and trimethylamine (38.73 mL, 278.6 mmol). The reaction mixture was stirred overnight in a sealed bottle. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water, made alkaline with 1 N sodium hydroxide to pH 10 and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 2-cyano-4-(dimethylamino)methylpyridine 92 (6.2 g): ESI MS m/z 162 [M + H]<sup>+</sup>.

## EXAMPLE SP-260

 $N^{1}$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[({4-

[(dimethylamino)methyl]

pyridin-2-yl}methyl)amino]-2-

20 hydroxypropyl}

 $-5-(1,3-oxazol-2-yl)-N^3,N^3-$ 

dipropylisophthalamide

Step 1: A mixture of 2-cyano-4-(dimethylamino)methylpyridine
92 (2.0 g, 12.4 mmol), 10% Pd/C (200 mg) and concentrated
hydrochloric acid (8 mL) in methanol (180 mL) was shaken under
60 psi hydrogen overnight. The reaction mixture was filtered
through diatomaceous earth and repeatedly washed with water
and methanol. Methanol was removed under reduced pressure and
the residue partitioned between water and methylene chloride.

The aqueous layer was made alkaline with 1 N sodium hydroxide
and extracted with methylene chloride. The organic layer was
washed with saturated sodium chloride, dried (sodium sulfate),
filtered, and concentrated under reduced pressure to give an
oil (1.07 g): ¹H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.53 (d, J = 5 Hz, 1H),

7.25 (s, 1H), 7.13 (d, J = 5 Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.26 (s, 6H); ESI MS m/z 166 [M + H]<sup>+</sup>.

Step 2: A mixture of the orange oil from step 1 (500 mg, 3.03 tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)and mmol) oxiran-2-yl]ethylcarbamate (907 mg, 3.03 mmol) in 2-propanol (20 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced residue was purified by flash column The pressure. chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to 10 give a solid (1.13 g): ESI MS m/z 465 [M + H]<sup>+</sup>.

Step 3: The yellow solid from step 2 (400 mg, 0.86 mmol) was dissolved in dioxane (4.3 mL) and hydrogen chloride (4.3 mL, 4 M dioxane, 17.22 mmol) was added. The reaction mixture was 15 stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and N, N-diisopropylethylamine (3 mL) were added. The organic phase was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under 20 reduced pressure to give an oil (365 mg): ESI MS m/z 365 [M + H1+

Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid 93 (173.6 mg, 0.55 mmol) and N,N-disopropyl ethylamine (191  $\mu\text{L}$ , 1.10 mmol) in methylene chloride (6.0 mL) was added HBTU (218.62 mg, 0.58 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of the orange oil from step 3 (300 mg, 0.823 mmol) and N,N-diisopropylethylamine (191  $\mu$ L, 1.10 mmol) 30 in methylene chloride (6.0 mL), and the reaction mixture was The reaction mixture was stirred under nitrogen for 18 h. then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, 0.5 N hydrochloric acid,

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and saturated sodium chloride,. The organic layer was then and concentrated under dried (sodium sulfate), filtered, Purification by reduced pressure to yield an oily residue. flash column chromatography (silica, 10:90 methanol/methylene  $N^{1} - \{ (1S, 2R) - 1 - (3, 5 - diffluorobenzy1) - 3 - [ ( \{4 - 1\}, 2R) - 1 - (3, 5 - diffluorobenzy1) - 3 - [ ( \{4 - 1\}, 2R) - 1 - (3, 5 - diffluorobenzy1) - 3 - [ ( \{4 - 1\}, 2R) - 1 - ( \{4 - 1\}, 2R) - ( \{$ αave chloride) pyridin-2-yl}methyl)amino]-2-[(dimethylamino)methyl]  $-5-(1,3-oxazol-2-yl)-N^3,N^3$ hydroxypropyl} dipropylisophthalamide (94) (233 mg): mp 65-68 °C; ESI MS m/z $663 [M + H]^{+}$ 

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EXAMPLE SP-261

 $N^{1}$ -{ (1S, 2R) -1- (3, 5-difluorobenzyl) -3-[(1-{4-Synthesis ofpyridin-2-yl}cyclopropyl)amino]-2-[(dimethylamino)methyl]  $hydroxypropyl\}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide$ 

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solution of 2-cyano-4-To а 1: Step (dimethylamino) methylpyridine 92 (prepared as in EXAMPLE SP-259) (500 mg, 3.10 mmol) in tetrahydrofuran (10 mL) was added 3.41 mmol) and (1.01)mL, titanium(IV) isopropoxide ethylmagnesium bromide (6.20 mL, 1 N THF, 6.20 mmol). stirring for 0.5 h, boron trifluoride diethyl etherate (786 μL, 6.20 mmol) was added in one portion. The reaction mixture was stirred for 1 h at room temperature and 1 N sodium hydroxide was added to adjust the mixture to pH 9-10.

white solid generated was removed by filtration and the filtrate was partitioned between water and methylene chloride. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (silica, 1:99 to 3:97 ammonium column hydroxide/2-propanol) gave an oil (360 mg): <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.42 (dd, J = 6, 5 Hz, 1H), 3.41 (s, 2H), 7.02 (dd, J= 6, 5 Hz, 1H), 3.98 (s, 2H), 3.42 (s, 2H), 2.25 (s, 6H), 2.08(s, 2H), 1.31-1.27 (m, 2H), 1.15-1.11 (m, 2H); ESI MS m/z 192 $[M + H]^{+}$ .

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- Step 2: A mixture of the oil from step 1 (350 mg, 1.83 mmol) and tert-butyl (1S)-2-(3,5-difluorophenyl)-1-[(2S)-oxiran-2-15 yl]ethylcarbamate (496.8 mg, 1.66 mmol) in 2-propanol (13 mL) was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica, 1:99 ammonium hydroxide/2-propanol) to give a solid (300 mg):

  20 ESI MS m/z 491 [M + H]<sup>+</sup>.
  - Step 3: To a stirred solution of the solid from step 2 (300 mg, 0.61 mmol) in dioxane (6.0 mL) was added hydrochloric acid (6.0 mL, 4 N dioxane, 24.40 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure and methylene chloride and N, N-diisopropylethylamine (3 mL) were added. The organic layer was washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an oil (269 mg): ESI MS m/z 391 [M + H]<sup>+</sup>.
    - Step 4: To a stirred solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid **93** (prepared as in EXAMPLE S-

2364, step 5) (124.3 mg, 0.39 mmol) and N, N-diisopropyl ethylamine (139 µL, 0.79 mmol) in methylene chloride (3.0 mL) was added HBTU (156.5 mg, 0.41 mmol) and the reaction mixture stirred for 0.5 h. To the above solution was added a solution of the orange oil from step 3 (269.6 mg, 0.823 mmol) and N, Ndiisopropylethylamine (139 µL, 0.79 mmol) in methylene chloride (3.0 mL), and the reaction mixture was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium 10 sulfate), filtered, and concentrated under reduced pressure to yield an oily residue. Purification by flash column 10:90 methanol/methylene chloride) chromatography (silica,  $N^{1}$ -{(1S, 2R)-1-(3, 5-diffuorobenzyl)-3-[(1-{4gave pyridin-2-yl}cyclopropyl)amino]-2-[(dimethylamino)methyl] 15  $hydroxypropyl\}-5-(1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide$ (95) (134 mg): mp 70-72 °C; ESI MS m/z 689 [M + H]<sup>+</sup>.

EXAMPLE SP-262

Preparation of bromo-cyclopropyl cyanide 2 (modification of procedure from Org. Prep. & Proc. Int., 1995, 27(3), 355)

A mixture of 1-bromo-2-chloroethane (BCE; 120 ml), 3-bromobenzyl cyanide (25 g) and benzyl-triethylammonium chloride (TEBAC, 1.1 g) was stirred at 40°C while base (50% NaOH, 120 g) was added dropwise over 20 min. Temperature has risen to ~80°C within first 15 min. Very vigorous mechanical

stirring was continued while temperature slowly dropped to 50°C (over the next 3 hr). The mixture was deep red at this stage. After 3 hr there was no starting material (TLC). The reaction mixture was cooled down to RT, water (100 ml) was added and stirred for 5 min. Organic layer was separated and aqueous was extracted with dichloromethane (3 x). Combined organic layers were washed with water and dil. aq. HCl. Solution was dried using MgSO<sub>4</sub>, filtered and concentrated yielding deep yellow oil (126 g; still contains some BCE). Product was purified by a high vacuum fractionation using short-path set-up and single receiver. Collected fraction with bp 108-115°C / 0.1-0.05 mmHg as a heavy oily liquid 26.6 g (94%). After cooling to RT this liquid solidified.

# 15 Preparation of bromoamide 3

Bromocyanide 2 (5.9 g; 26.6 mmol) was dissolved in methanol (150 ml). To this solution while stirring KOH (25% aq soln., 0.68 ml) and hydrogen peroxide (30%, 35 ml) was added and the reaction mixture was heated at 55°C for 5 hr. At that time there was no starting material (TLC). Mixture was evaporated yielding solid residue (7.1 g; contains KOH).

# Preparation of bromoacid 4

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Crude bromoamide 3 from previous reaction was slurried in methanol (10 ml) and NaOH (10% aq, 150 ml) was added. Reaction mixture was refluxed 4.5 hr (TLC control). The mixture was cooled to RT, acidified with 15% HCl (to pH 2) and concentrated. Precipitated white solid was collected by filtration. Yield 6.8 g.

Preparation of acid chloride **5** (slight modification of procedure from Synlett 1999, 11, 1763)

Thionyl chloride (2.73 ml) and benzotriazole (4.47 g) were dissolved in dry dichloromethane (25 ml). Crude bromoacid 4 (6.8 g) was dissolved in dichloromethane (120 ml) and to this stirred solution the prepared above thionyl chloride solution (22.2 ml; 1.25 eq) was added portionwise over a few minutes. Before the addition was complete, benzotriazole hydrochloride started separating out as a white solid. The reaction mixture was stirred for additional 15 min and at the end the solids were filtered off. Filtrate was stirred with anhydrous MgSO<sub>4</sub> (2 g) to destroy an excess of reagent. The solids were filtered off and filtrate was evaporated and dried under high vacuum for 1 hr to give viscous amber oil. Yield 6.6 g.

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# Preparation of bromoamine 6

Crude acid chloride 5 was dissolved in dry acetone (40 ml), cooled to -10°C and treated with sodium azide (4 g in 15 ml of waterl). After stirring for 1 hr at -10°C a mixture was 20 allowed to warm to 0°C and was poured into cold water (300 ml). Azide was extracted into smallest possible amount of toluene (ca. 40 ml). The toluene layer was washed with water and dried. Solids were filtered off and resulting solution was stirred and heated cautiously at 100°C for 1 hr. Conc. HCl (~ 25 25 ml) was added through condenser and mixture was refluxed for 15 min. On cooling white crystalline material precipitated and was filtered off. Filtrate was slightly concentrated, cooled down and additional portion of precipitate collected. Combined solids were dried to give 4.1 g of bromo-30 cyclopropylamine 6 as hydrochloride salt.

Preparation of compound 7

Crude bromoamine hydrochloride **6** (2 g; 8 mmol) was dissolved in sat. aq Na<sub>2</sub>CO<sub>3</sub> (20 ml) and extracted with dichloromethane (5 x 10 ml). Combined extracts were dried, evaporated and kept overnight under vacuum. Yield of bromoamine **6** (1.68 g, 7.92 mmol). This amine was dissolved in isopropanol (20 ml) and epoxide (ii; 2.36 g, 7.92 mmol) was added. A mixture was stirred in a sealed tube at 80°C until starting epoxide was not detected by TLC (2-6 hr). Reaction mixture was cooled and solvent was evaporated to give, after drying under vacuum, white solid (3.9 g, 82 % pure).

# Preparation of compound 8

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Crude BOC bromide 7 (3.9 g; 7.0 mmol; 1 eq) was dissolved in triethylamine (20 ml) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.196 g, 0.28 mmol; 15 0.04 eq) and CuI (0.068 g; 0.36 mmol; 0.05 eq) were added. Upon addition of CuI a reaction mixture turned yellow then changed color slowly to green. The reaction mixture was heated orange-brown. point it turned which reflux, at Trimethylsilyl acetylene (0.82 g, 1.2 ml, 8.2 mmol, 1.2 eq) 20 was added via syringe. A black precipitate formed immediately. The reaction mixture was refluxed for 3 hr under nitrogen, then it was cooled to RT before partitioning between aq. sat.  $\mathrm{Na_{2}CO_{3}}$  and ethyl acetate. Organic layer was separated and aqueous was extracted with ethyl acetate (3  $\times$  25 ml). Combined 25 extracts were washed with brine, dried and evaporated. The crude product was contaminated by acetylene derived from bromoamine 6.

# 30 Preparation of BOC-acetylene 8a

To a solution of crude silyl-protected acetylene 8 (from previous reaction) in THF (5 ml) the tetrabutylammonium fluoride (1M in THF, 8 ml) was added. Mixture was stirred for

1 hr at RT, solvent was evaporated, residue was dissolved in ether (30 ml), washed with brine, dried and concentrated. Crude product was purified by flash chromatography on silica gel using ethyl acetate/hexane (2:3) mixture to give purified BOC-acetylene 8a (1.54 g, 43% from 6).

Preparation of 9:

1-(3,5-difluorobenzyl)-3-[1-(3-ethynylphenyl)cyclopropylamino)]-2-hydroxypropyl amine

10 dihydrochloride

[1-(3,5-difluorobenzyl)-3-[1-(3-

ethynylphenyl)cyclopropylamino]-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.34 g, 5.13 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3. mmol). The resulting heterogeneous mixture was treated with methanol (10 mL) whereupon it became homogeneous over 30 min.. The volatiles were evaporated in vacuo. Dioxane (20 mL) was added and the mixture was evaporated in vacuo to produce a white solid (2.33 g, 106%).

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EXAMPLE SP-263

Preparation of cyclopropyl m-ethylbenzylamine (11)

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Preparation of 10.

1-(3-Bromo-phenyl)-cyclopropylamine 6 (25 g, 112 mmol), triethylamine(21.7g, 2170 mmol) were mixed together in  $CH_2Cl_2$  (300 mL). The solution was cooled to 0 °C and box anhydride (25.07 g, 115 mmol) added in 4 equal portions at 15 minute

intervals. (Gas evolution noted after each addition). Mixture stirred for 30 minutes and then an additional 5 grams of boc anhyrdide was added to drive reaction to completion (GC/MS). Solution worked up with 1 N HCl (2X 100 mL), saturated aq. sodium bicarbonate (2 X 100 mL), and dried over sodium sulfate. Solvent was removed at reduced pressure and product was isolated by crystallization from cold hexanes (about 150 mL). Obtained 20.6 grams of white solid. Reduced volume of hexanes to about 75 ml and second crop was obtained (9.2 g)

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Preparation of 11.

The Boc-bromobenzyl amine 10 (26.8 g, 94.03 mmol), and PddfPdCl<sub>2</sub> (816 mg, 0.38 mmol, 0.004 eq) were mixed together in anhydrous THF (300 mL) and aqueous  $K_3PO_4$  (100 mL of 2.0 M). To 15 this red solution was added triethylborane (100 ml of 1.0 M in THF, 100 mmol). The solution turned black and was refluxed for 4 hours. GC/MS indicated the reaction was complete. The solution was poured into a separatory funnel and the aqueous layer separated. The organic layer was collected and solvent 20 removed to a volume of 100 mL. Ethyl acetate/ hexanes (300 mL of 1:1) were added and the solution was extracted with 1N HCl (1X100 mL), sodium bicarbonate (2X 100 mL) and brine (1X100 mL). The solution was dried over sodium sulfate and vacuum 25 filtered through a bed of silica gel ( 125 ml of silica). The solvent was removed at reduced pressure to afford 20.6 grams of 11 as light yellow oil.

# EXAMPLE SP-264

30 Preparation of 6-Methyl-pyridine-2,4-dicarboxylic acid 4-({1-(3,5-difluoro-benzyl)-3-[1-(3-ethynyl-phenyl)-cyclopropylamino]-2-hydroxy-propyl}-amide) 2-dipropylamide

The Boc protected amine (prepared as in EXAMPLE SP-262) (0.912 g, 2 mM) was treated with 50% TFA in  $CH_2Cl_2$  (1 hr, RT). Solvents were removed under reduced pressure to form an oil. 5 Added toluene and evaporated; repeated stripping with toluene. After this operation and keeping residue under high vacuum for 1 hr off-white solid was obtained (free amine, most likely as a TFA salt). This amine was dissolved in CH2Cl2 (10 mL, slurry), added acid 2 (0.528 g; 2 mM), HOBt (0.297 g; 2.2 mM) 10 and EDC (0.423 g; 2.2 mM). When EDC was added slurry rapidly became clear solution. At the end an excess of NEt3 (2 mL) was added and a reaction mixture was stirred o/n at RT. The next day solvent was stripped and EtOAc solution was washed with 15 saturated solution of Na<sub>2</sub>CO<sub>3</sub> (3x), brine, dried and concentrated. Initially purified by flash chromatography on Biotage (eluted with 20% hexane and 80% EtOAc). Final purification was done by HPLC. The TFA salt was converted into HCl mono salt by addition of 1.25M solution of HCl in MeOH 20 (1.6 mL). Yield 0.971 g (76%).

# EXAMPLE SP-265

N<sup>1</sup>-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-25 2-yl)-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide;

The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 659.3.

5 Carbon NMR (CDCl<sub>3</sub>): 11.00, 11.56, 11.78, 15.37, 20.80, 21.90, 28.71, 35.28, 44.45, 47.26, 49.97, 51.16, 53.75, 69.43, 77.12, 102.12, 112.02, 112.34, 126.23, 126.94, 127.29, 128.01, 128.68, 129.20, 129.51, 133.90, 134.70, 137.56, 139.59, 142.15, 145.53, 160.26, 161.43, 164.73, 166.98, 170.42.

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#### EXAMPLE SP-266

 $N^{1}$ -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)- $N^{3}$ ,  $N^{3}$ -dipropylisophthalamide

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The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 655.3.

Carbon NMR (CDCl<sub>3</sub>): 11.01, 11.47, 11.58, 11.98, 20.82, 21.91, 35.22, 43.94, 47.28, 50.09, 51.17, 53.77, 69.49, 77.11, 78.63, 82.55, 102.17, 112.05, 123.22, 126.23, 126.82, 128.07, 128.76,

129.49, 130.68, 133.33, 134.50, 137.57, 139.61, 142.17, 160.23, 161.27, 164.56, 167.04, 170.44.

#### EXAMPLE SP-267

5 N<sup>4</sup>-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-6-methyl-N<sup>2</sup>,N<sup>2</sup>-dipropylpyridine-2,4-dicarboxamide

The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+607.3

Carbon NMR (CDCl<sub>3</sub>): 10.96, 11.06, 11.53, 12.09, 15.43, 20.73, 21.90, 23.96, 28.75, 33.93, 44.32, 47.82, 49.60, 50.90, 53.98, 68.65, 77.11, 101.98, 112.064, 112.39, 117.03, 122.12, 127.25, 129.23, 129.49, 134.06, 142.21, 145.61, 153.63, 158.94, 161.19, 161.36, 164.48, 164.65, 165.65, 169.06.

# EXAMPLE SP-268

 $N^4$ -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-

20 ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide

The above identified compound is prepared essentially using the procedure described in EXAMPLE SP-264.

M+ 603.3.

Carbon NMR (CDCl<sub>3</sub>): 10.99, 11.58, 12.29, 20.75, 21.92, 24.03, 33.98, 43.91, 47.91, 49.83, 50.96, 53.95, 68.74, 77.13, 78.72, 82.57, 102.08, 112.08, 112.41, 117.63, 122.16, 123.32, 129.51, 130.66, 133.37, 133.55, 134.63, 142.28, 153.56, 158.96, 161.20, 161.37, 164.66, 165.80.

EXAMPLE SP-269

10 Preparation of 1-(3,5-difluorobenzyl)-3-(3-ethynyl)benzylamino)-2-hydroxypropyl amine dihydrochloride

[1-(3,5-difluorobenzyl)-3-(3-ethynylbenzylamino)-2-hydroxypropyl]-carbamic acid tert-butyl ester (2.73 g, 6.33 mmol) was treated with 4N HCl in dioxane (15.8 mL, 63.3. mmol). The mixture became homogeneous after 5 min and then deposited a precipitate. Diethyl ether (15 mL) was added to aid stirring and the mixture was stirred for 2 h. The volatiles were evaporated in vacuo. Dioxane (20 mL) was added and the mixture was evaporated in vacuo to produce a white solid (2.67 g, 104%).

EXAMPLE SP-270

N<sup>1</sup>-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N<sup>3</sup>,N<sup>3</sup>-dipropylisophthalamide

5-Ethynyl-N,N-dipropyl-iso-phthalamic acid (1.73 g, 6.32 5 mmol) was dissolved in anhydrous DMF (20 ml) under nitrogen. 1-Hydroxybenzotriazole (1.28 g, 9.48 mmol) dimethylaminopropy)-3-ethylcarbodiimidehydrochloride (1.70 g, 8.85 mmol)) were added in succession. This mixture was stirred for 30 min at RT until homogeneous and then was added in one 10 portion to a rapidly-stirred slurry of amine dihydrochloride (2.67, 6.32 mmol) and N-methylmorpholine ( 2.78 mL, 2.56 g, 25.3 mmol) in DMF (25mL). The resulting mixture was stirred for 2 h before diluting with saturated aq sodium bicarbonate The mixture was extracted with ethyl acetate (3 X 15 100 mL) and the combined organic extracts were washed with saturated ag sodium bicarbonate (100 mL), water (2 X 100 mL), and brine (100 mL), dried (sodium sulfate), filtered and evaporated in vacuo to give an oil (3.7 g). The product was purified using flash column chromatography on silica gel 20 (Flash 65i cartridge, eluting with 1L 100% ethyl acetate, then 4L 95:5 ethyl acetate/methanol ) to yield a pale yellow oil (2.74 g, 74%). LC-MS (m/e): 586 (M+1); 100% (254 nm). 152006 free base was dissolved in ethanol (25 mL) and treated with 4N HCl in dioxane (2.0 mL). The resulting mixture was 25 evaporated in vacuo to remove volatiles, re-dissolved in 1:1 ethanol/water (25 mL) and evaporated in vacuo. The resulting solid was slurried in diethyl ether (50 mL), filtered and washed with diethyl ether to produce an off-white solid which

was vacuumed dried to constant weight (2 d) to yield the desired product (2.43 g).

Analysis: for  $C_{35}H_{37}F_2N_3O_3$  +HCl: calcd.: C, 67.57; H, 6.16; N, 6.75; Cl, 5.50; found: C, 67.21; H, 6.04; N, 6.55; Cl, 5.71.

#### EXAMPLE SP-271

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Preparation of  $N^1$ -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methyl- $N^3$ ,  $N^3$ -dipropylisophthalamide

5-Methyl-N, N-dipropyl-iso-phthalamic acid (1.35 g, 5.13 mmol, was dissolved in anhydrous DMF (15 ml) under nitrogen. 1-Hydroxybenzotriazole (1.04 g, `7.69 mmol) and 15 dimethylaminopropy)-3-ethylcarbodiimide hydrochloride (1.38 g, 7.18 mmol)) were added in succession. This mixture was stirred for 30 min at RT until homogeneous and then was added in one portion to a rapidly-stirred slurry of amine dihydrochloride (2.23 g, 5.13 mmol) and N-methylmorpholine (2.25 mL, 2.07 g,20 20.5 mmol) in DMF (20 mL). The resulting mixture was stirred for 3.5 h before diluting with saturated aq sodium bicarbonate The mixture was extracted with ethyl acetate (3 X (150 mL). 100 mL) and the combined organic extracts were washed with saturated aq sodium bicarbonate (100 mL), water (2 X 100 mL), 25 and brine (100 mL), dried (sodium sulfate), filtered and evaporated in vacuo to give an oil (3.0 g). The product was silica gel purified using flash column chromatography on eluting with 2.8L 1:1 ethyl (Flash 65i cartridge, acetate/hexane, 2.5L 2:1 ethyl acetate/hexane, then 2L 100% 30

ethyl acetate) to yield a clear oil (2.34 g, 76%). LC-MS (m/e): 602 (M+1); 100% (254 nm). The ELN 152227 free base was dissolved in ethanol (25 mL) and treated with 4N HCl in dioxane (2.0 mL). The resulting mixture was evaporated in vacuo to remove volatiles, re-dissolved ethanol (25 mL) and evaporated in vacuo. The resulting solid was slurried in diethyl ether (50 mL) and filtered to produce a hygroscopic solid which was lyophilized to yield ELN 152227-3 (1.93 g). Analysis: for C<sub>36</sub>H<sub>41</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub> +HCl + 0.8 H<sub>2</sub>O: calcd.: C, 66.26; H, 6.73; N, 6.44; Cl, 5.43; found: C, 67.21; H 6.40; N, 6.42; Cl, 5.34.

#### EXAMPLE SP-272

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Preparation of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-15 ethylbenzyl)amino]butan-2-ol dihydrochloride

[1-(3,5-difluorobenzyl)-3-(3-The slurry οf ethylbenzylamino) -2-hydroxypropyl]-carbamic acid tert-butyl ester (5.25 g, 0.012 m) in anhydrous dioxane (20 ml) was stirred (magnetic bar) at RT under nitrogen atmosphere in an 250 ml round-bottom flask, immersed in a cold water bath. The solution of hydrogen chloride in dioxane (4M, 32 ml) was added in one portion. The reaction mixture, initially homogenous, became a thick slurry within ca. 20 min. Mixture was stirred for 70 min, and was monitored by the TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate - methanol 95:5 mixture). Ethyl ether (100 ml) was added, precipitated product was filtered off and rinsed with ether (2 x 50 ml). The filter cake was air-dried for 1 hour then placed in an vacuum oven at

35 °C and the oven evacuated (5 torr). Product was dried to constant mass for 7 hours. Yield was 5.24 g. LC-MS (m/e): 335 (M+1); purity: 100% (254 nm).

## 5 EXAMPLE SP-273

 $N^1-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-5-ethynyl-N^3,N^3-dipropylisophthalamide$ 

10 The 5-ethynyl-N,N-dipropyl-iso-phthalamic acid 0.006m) was dissolved in anhydrous DMF (30 ml) in an roundbottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBt (1.23 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added. This mixture was stirred for 45 min at RT and then was added 15 in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that time all solids gradually dissolved, mixture remained however 20 cloudy. Reaction progress was monitored by TLC (silica gel plates, 5 x 10 cm, eluted with ethyl acetate-methanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with ethyl acetate (3 x 150 ml). Combined extracts were washed with 25 brine and dried over magnesium sulfate. Solution was filtered and evaporated, yield of crude product was 4.6 g (yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane

solution and eluted with ethyl acetate-methanol 93:7 mixture). Fractions containing product were combined and evaporated to give pale yellow oil, 2.7 g. LC-MS (m/e): 590 (M+1); 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq), filtered and lyophilized. Yield of final hydrochloride salt was 2.4 g. LC-MS (m/e) 590 (M+1); purity: 100% (254 nm), 100% (280 nm).

<sup>1</sup>H-NMR (MeOH-d4):  $\delta$  0.70 (t, 3H), 1.01 (t, 3H), 1.23 (t, 3H), 1.53 (m, 2H), 1.73 (m, 2H), 2.67 (q, 2H), 2.87 (m, 1H), 3.05-3.35 (m, 8H), 4.00 (s, 1H), 4.01 (m, 1H), 4.25 (m, 3H), 4.91 (s), 6.77 (m, 1H), 6.91 (d, 2H), 7.29-7.38 (m, 4H), 7.56 (d, 2H), 7.79 (s, 1H).

<sup>13</sup>C-NMR: (MeOH-*d4*): 9.73, 10.17, 20.17, 21.33, 46.51-48.32, 49.27, 50.71, 54.04, 68.75, 79.79, 80.94, 101.17 (t), 111.56 (d), 123.26, 124.83, 127.00, 128.73, 129.23, 130.53, 130.95, 132.15, 134.29, 137.46, 142.69, 142.81, 145.17, 161.28 (d), 164.40 (d), 167.13, 170.28.

Analysis: for  $C_{35}H_{42}ClF_2N_3O_3 \times 0.5 H_2O$  calcd.: C, 66.18; H, 6.82; N, 6.62; Cl, 5.58; found: C, 66.07; H 6.85; N, 6.79; Cl, 5.17.

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#### EXAMPLE SP-274

Preparation of  $N^1-\{(1S,2R)-1-(3,5-\text{difluorobenzyl})-3-[(3-\text{ethylbenzyl})\,\text{amino}]-2-\text{hydroxypropyl}\}-N^3,N^3-\text{dipropyl}-5-(1,3-\text{thiazol}-2-yl)\,\text{isophthalamide}$ 

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The N,N-dipropyl-5-thiazol-2-yl-iso-phthalamic acid (1.99 g, 0.006m) was dissolved in anhydrous DMF (30 ml) in an round-

bottom flask (50 ml) equipped with magnetic stirring bar. Flask was flushed with nitrogen and HOBt (1.24 g, 0.009m, 1.5 eq), followed by EDC (1.63 g, 0.0084m, 1.4 eq) were added. This mixture was stirred for 45 min at RT and then was added in one portion to the stirred solution of amine hydrochloride (2.45 g, 0.006m) in anhydrous DMF (30 ml) and NMO (5.0 g, 0.05m, 8.5 eq). The resulted heterogeneous mixture was vigorously stirred under nitrogen at RT for 2 hr. During that time all solids gradually dissolved, mixture remained however slightly cloudy. Reaction progress was monitored by TLC 10 (silica gel plates, 5 x 10 cm, eluted with ethyl acetatemethanol 95:5 mixture). Product was isolated by diluting reaction mixture with sat. aq. sodium bicarbonate (250 ml) and extraction with ethyl acetate  $(3 \times 150 \text{ ml})$ . Combined extracts were washed with brine and dried over magnesium sulfate. 15 Solution was filtered and evaporated, yield of crude product was 4.2 g (pale yellow oil). Product was purified using flash column chromatography on silica gel (Flash 65i cartridge, applied in dichloromethane solution and eluted with ethyl acetate-methanol 9:1 mixture). Fractions containing product 20 were combined and evaporated to give pale yellow oil, 2.75 g. (m/e): 649 (M+1); purity: 100% (254 nm). Purified product was treated with ethanolic hydrogen chloride (1.05 eq) and lyophilized (added ethanol to improve solubility before 25 filtration). Yield of final hydrochloride salt was 2.6 g. LC-MS (m/e): 649 (M+1); purity: 100% (254 nm).  $^{1}\text{H-NMR}$  (MeOH-d4):  $\delta$  0.74 (t, 3H), 1.04 (t, 3H), 1.20 (t, 3H), 1.58 (m, 2H), 1.77 (m, 2H), 2.64 (q, 2H), 2.92 (m, 1H), 3.10-3.55 (m, 9H), 4.04 (m, 1H), 4.26 (m, 2H), 4.90 (s), 6.77 (m, 2H)1H), 6.96 (d, 2H), 7.23-7.38 (m, 4H), 7.68 (t, 1H), 7.73 (d, 30 1H), 7.96 (d, 1H), 8.11 (t, 1H), 8.28 (t, 1H).

 $^{13}$ C-NMR: (MeOH-d4): 9.76, 10.19, 14.75, 20.21, 21.39, 28.10, 35.38, 46.60-48.31, 50.75, 54.12, 68.78, 101.22 (t), 111.53 (d), 120.48, 125.65, 126.12, 126.97, 128.70, 129.218, 130.56,

133.96, 134.97, 138.00, 142.84, 143.53, 145.16, 161.31 (d), 164.52 (d), 165.96, 167.36, 170.47.

Analysis: for  $C_{36}H_{43}ClF_2N_4O_3S \times 0.5 H_2O$  calcd.: C, 62.28; H, 6.39; N, 8.07; Cl, 5.11; found: C, 62.42; H 6.24; N, 8.03; Cl, 5.10.

#### EXAMPLE SP-275

2-Dipropylcarbamoyl-6-methyl-isonicotinic acid

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Commercially available, 2-chloro-methylisotinic acid (4.07g, 23.72 mmol) was dissolved in a 30%MeOH/ THF solution (32 ml). (Trimethylsilyl)diazomethane (2.0 M solution in hexanes) was added dropwise. Bubbling was observed and more reagent was added until bubbling ceased (15mL). The reaction mixture was allowed to stir overnight at room temp. Prior to evaporation of solvent, glacial acetic acid was added to the reaction flask dropwise in order to rid of excess amine.

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EXAMPLE SP-276

Reference: Fuqiang, J. and Confalone, N. Tet. Lett., 41, 2000, 3271-3273

25 Into a R.B flask equipped with a stir bar was added the methylated intermediate, tri(dibenzlideneacetone)dipalladium

(0), 1,1-bis(diphenylphosphine), zinc metal dust and zinc cyanide. The flask was flushed with nitrogen gas for approx. 5 min. N,N-dimethylacetamide was added via syringe. The reaction mixture was refluxed in an oil bath set at 120°C with a condenser under nitrogen atmosphere. Stir vigorously. After 4 h, the reaction mixture was partitioned between ethyl acetate (50 ml) and 2N NH<sub>4</sub>OH (50 ml) Repeat washing with 2N NH<sub>4</sub>OH (2 x 50 ml) followed by brine (50 ml). Organic phases were collected and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. Purification by column chromatography was performed with eluting solvent (80:20;Hex/EtOac).

# EXAMPLE SP-277

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Dissolve nitrile intermediate (0.206g, 1.170 mmol) in methanol (5 ml). Add sodium hydroxide (0.267g, 6.675 mmol) and continue to stir at room temp. After 90 min add water (5 ml) and continue to stir for an additional 90 min. Partition between chloroform and 2 N HCl (aq). Add NaCl(s) to aqueous phase in order to saturate. Continue extraction with isopropanol:chloroform (1:3). Collect organic phases, dry over NaSO<sub>4</sub>, filter and evaporate.

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EXAMPLE SP-278

Anhydrous dichloromethane was added to the hydrolyzed intermediate (0.136, 0.697 mmol) followed by 4-methylmorpholine. The flask was placed on an ice bath to cool prior to addition of HBTU and dipropylamine. The mixture was allowed to warm to room temp. over night under nitrogen atmosphere. Partition reaction mixture between ethyl acetate (25 ml) and water (25 ml). Wash with water followed by sat. NaHCO<sub>3</sub> (2 x 25 ml). Organic phase was collected, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated.

EXAMPLE SP-279

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15  $N^1-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-5-(4-methyl-1,3-oxazol-2-yl)-N^3,N^3-dipropylisophthalamide$ 

Step 1: A stirred solution of methyl 3-(aminocarbonyl)-5[(dipropylamino)carbonyl]benzoate (200 mg, 0.65 mmol)
chloroacetone (10 mL, 93 mmol) and potassium carbonate (90 mg,
0.65 mmol) was refluxed for 18 h. The reaction mixture was
cooled to room temperature, diluted with ethyl acetate, washed
with 2 N sodium hydroxide (2 x 50 mL), and saturated sodium

chloride, dried (magnesium sulfate), and concentrated under
reduced pressure. Purification by flash column chromatography
(silica, 1:1 ethyl acetate/hexanes) provided methyl 3[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoate

5 (119 mg): ¹H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.70 (d, J = 1 Hz, 1H),
8.20 (d, J = 1 Hz, 1H), 8.09 (d, J = 1 Hz, 1H), 7.48 (s, 1H),
3.96 (s, 3H), 3.46 (d, J = 7 Hz, 2H), 3.16 (t, J = 7 Hz, 2H),
2.26 (s, 3H), 1.71 (d, J = 7 Hz, 2H), 1.54 (d, J = 7 Hz, 2H),
1.00 (t, J = 7 Hz, 3H), 0.74 (t, J = 7 Hz, 3H); ESI MS m/z 345

Step 2: A solution of methyl 3-[(dipropylamino)carbonyl]-5-(4methyl-1,3-oxazol-2-yl)benzoate (118 mg, 0.34 mmol) methanol (1 mL) and potassium hydroxide (1 mL of a 1.0 M solution in water, 1 mmol) was stirred at room temperature for 15 The solvent was removed under reduced pressure, the 45 min. residue was dissolved in water, extracted with ethyl acetate, the aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined 20 organics were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (110 mg): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.66 (d, J = 1 Hz, 1H), 8.17 (d, J = 1 Hz, 1H), 8.07 (d, J = 1 Hz, 1H), 7.75 (d, J = 1 Hz, 1 H, 3.51 (t, J = 7 Hz, 2 H), 3.25 (t, J = 7 Hz, 2 H),2.23 (s, 3H), 1.74 (d, J = 7 Hz, 2H), 1.60 (d, J = 7 Hz, 2H), 25 1.01 (t, J = 7 Hz, 3H), 0.76 (t, J = 7 Hz, 3H).

Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(4-methyl-1,3-oxazol-2-yl)benzoic acid (77.5 mg, 0.23 mmol), (2R,3S)-3-30 amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (96 mg, 0.23 mmol), HOBt (32 mg, 0.23 mmol), and N-methylmorpholine (83 µL, 0.75 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (73 mg, 0.42 mmol) was added and the reaction mixture was stirred overnight. The

reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by 5 flash column chromatography (silica, 1:9 methanol/chloroform)  $N^{1}-\{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-mathemathem)]$ provided ethylbenzyl)amino]-2-hydroxypropyl}-5-(4-methyl-1,3-oxazol-2 $y1)-N^3$ ,  $N^3$ -dipropylisophthalamide (40 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.20 (br s, 1H, -NH), 8.17 (s, 1H), 8.05 (s, 1H), 7.52 (s, 1H), 7.38 (s, 1H), 7.24-7.08 (m, 5H), 7.02 (d, J = 8 Hz)2H), 6.61 (t, J = 8 Hz, 1H), 4.27 (br s, 1H), 3.93 (d, J = 4Hz, 1H), 3.85 (s, 2H), 3.54 (br s, 2H), 3.43 (br s, 2H), 2.84 (d, J = 5 Hz, 2H), 2.63 (q, J = 8 Hz, 2H), 2.18 (s, 3H), 1.74(t, J = 5 Hz, 2H), 1.41 (d, J = 7 Hz, 2H), 1.22 (t, J = 8 Hz,15 3H), 1.03 (t, J = 7 Hz, 3H), 0.64 (t, J = 7 Hz, 3H); ESI MS m/z 647 [M + H]<sup>+</sup>

## EXAMPLE SP-280

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 $N^1$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^3$ ,  $N^3$ -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide

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Step 1: To a -78 °C solution of thiazole (1.2 g) in THF (25 mL) was added n-butyl lithium (1.6 M in hexanes, 10 mL). The mixture was stirred for 30 min and then allowed to warm to 0 °C

in an ice/water bath. Zinc chloride (1M in ethyl ether, 40 mL) was added and the mixture was stirred for 1 h, at which time methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (5.1 g) in THF (20 mL) was added, followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (palladium tetrakis triphenylphosphine) (0.68 g). The mixture was then heated at 80 °C for 2 h, at which time it was allowed to cool and partitioned between ethyl acetate and water. The organic layers were washed with brine, dried (magnesium sulfate), and concentrated. The residue was chromatographed on silica gel using ethyl acetate/heptane (50/50) to give 4.5 g of methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate.

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- Step 2: Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate (4.5 g) was dissolved in THF (20 mL), methanol (20 mL), and water (20 mL). Lithium hydroxide monohydrate (1.1 g) was added and the mixture was stirred at room temperature for 1.5 h, at which time the organic solvents were removed under reduced pressure. Some ethyl acetate and water were added and the pH was adjusted to about 0 with aq. HCl. The mixture was extracted with ethyl acetate and the organic layers were washed with brine, dried (magnesium sulfate), and concentrated to give 3.8 g of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid
- Step 3: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid (156 mg, 0.47 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (191 mg, 0.47 mmol), HOBt (64 mg, 0.47 mmol), and N-methylmorpholine (200 μL, 1.5 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (145 mg, 0.84 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 N hydrochloric acid (25 mL), saturated sodium bicarbonate

(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform)  $N^{1}$ -{(1S, 2R)-1-(3,5-diffuorobenzyl)-3-[(3provided ethylbenzyl)amino]-2-hydroxypropyl}-N3,N3-dipropyl-5-(1,3thiazol-2-yl)isophthalamide (33 mg):  $^1\text{H}$  NMR (500 MHz, CDCl3)  $\delta$ 8.40 (br s, 1H, -NH), 8.15 (br s, 1H), 7.94 (br s, 1H), 7.80 (d, J = 3 Hz, 1H), 7.51 (br s, 1H), 7.34 (d, J = 3 Hz, 1H),7.27-7.24 (m, 1H), 7.21-7.18 (m, 2H), 7.11-7.10 (m, 1H), 7.00(br s, 1H), 6.62-6.58 (m, 1H), 4.23 (d, J = 5 Hz, 1H), 3.91-10 3.85 (m, 3H), 3.57 (br s, 2H), 3.31 (br s, 2H), 3.05 (d, J=5)Hz, 4H), 2.83 (d, , J = 6 Hz, 2H), 2.64 (q, J = 8 Hz, 2H), 1.75 (br s, 2H), 1.44 (t, J = 7 Hz, 2H), 1.22 (t, J = 8 Hz, 3H) 1.04 (t, J = 7 Hz, 3H), 0.65 (t, J = 7 Hz, 3H); ESI MS m/z $649 [M + H]^+;$ 15

#### EXAMPLE SP-281

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 $N^{1}$ -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2hydroxypropyl}-5-(1,3-oxazol-2-yl)- $N^{3}$ , $N^{3}$ -dipropylisophthalamide

Step 1. To an ice-cold, stirred solution of 3-amino-5-(methoxycarbonyl)benzoic acid (5.19 g, 26.59 mmol) in a 2 N hydrochloric acid (156 mL) was added a solution of sodium nitrite (1.84 g, 26.67 mmol) in water (10.8 mL). This mixture was then added dropwise to an ice-cold, stirred solution of potassium iodide (8.84 g, 53.25 mmol) in water (26.2 mL).

After stirring for 35 min, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium thiosulfate, and saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash chromatography (silica, 50:50:2 hexanes/ethyl column acetate/acetic acid) afforded 3-iodo-5-(methoxycarbonyl)benzoic acid (4.48 g): <sup>1</sup>H NMR (500 MHz, DMSO $d_6$ ):  $\delta$ 13.49 (br s, 1H), 8.45-8.38 (m, 3H), 3.83 (s, 3H); ESI-MS  $(m/z): 305 [M + H]^+.$ 

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Step 2: To a mixture of 3-iodo-5-(methoxycarbonyl)benzoic acid (65.8 g, 0.215 mol), triethylamine (52.2 g, 0.516 mol), and dipropylamine (23.9 g, 0.237 mol) in methylene chloride (950 mL) was added 2-chloro-1-methylpyridinium iodide (65.9 g, 15 0.258 mol). The reaction mixture was stirred at temperature for 15 h and then concentrated under reduced pressure. Purification by silica gel plug (3:1 hexanes/ethyl provided methyl 3-[(dipropylamino)carbonyl]-5acetate) 20 iodobenzoate (66.8 g):  ${}^{1}NMR$  (300 MHz, CDCl3)  $\delta$  8.39 (s, 1H), 7.98 (s, 1H), 7.88 (s, 1H), 3.93 (s, 3H), 3.45 (m, 2H), 3.14 (m, 2H), 1.69 (m, 2H), 1.54 (m, 2H), 0.98 (m, 3H), 0.77 (m, 3H).

25 Step 3: A stirred solution of 2-triethylstannyloxazole (Chem. Mater. 1994, 6, 1023)(1.5 g, 5.5 mmol) and methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (1.8 g, 4.6 mmol) in dimethylformamide (12 mL) was degassed under reduced pressure and purged with argon. Palladium(0) for 15 min tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) was added and 30 the reaction mixture was degassed under reduced pressure for 15 min and then purged with argon. The reaction mixture was heated at reflux for 2 d, cooled to room temperature, diluted with ethyl acetate, washed with water (3 x 50 mL), dried

(sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoate (423 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.73 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H), 7.28 (s, 1H), 3.97 (s, 3H), 3.49 (br s, 2H), 3.18 (br s, 2H), 1.72 (d, J=7 Hz, 2H), 1.55 (d, J=7 Hz, 2H), 1.00 (t, J=7 Hz, 3H), 0.75 (t, J=7 Hz, 3H).

- Step 4: A solution of methyl 3-[(dipropylamino)carbonyl]-5-10 (1.3-oxazol-2-yl) benzoate (315 mg, 0.95 mmol) in methanol (3mL) and potassium hydroxide (3 mL of a 1.0 M solution in water, 3 mmol) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, the residue was dissolved in water, and extracted with ethyl acetate. The 15 aqueous layer was acidified to pH 3 with 1 M hydrochloric acid, extracted with chloroform (3 x 100 mL), and the combined organic layers were concentrated under reduced pressure to afford 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (265 mg):  $^{1}$ H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.71 (s, 1H), 8.08 (s, 20 2H), 8.05 (s, 1H), 7.34 (s, 1H), 3.52 (t, J = 8 Hz, 2H), 3.26 (t, J = 8 Hz, 2H), 1.75 (q, J = 8 Hz, 2H), 1.59 (q, J = 8 Hz,2H), 1.02 (t, J = 8 Hz, 3H), 0.74 (t, J = 8 Hz, 3H).
- Step 5: A solution of 3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoic acid (133 mg, 0.42 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride (171 mg, 0.42 mmol), HOBt (57 mg, 0.42 mmol), and N-methylmorpholine (148 μL, 1.3 mmol) was stirred in dimethylformamide (2 mL) for 15 min. EDC (130 mg, 0.75 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with 1 M hydrochloric acid (25 mL), saturated sodium bicarbonate

(25 mL), saturated sodium chloride, dried (sodium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform)  $N^{1}$ -{(1S, 2R)-1-(3, 5-difluorobenzyl)-3-[(3provided ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-oxazol-2-yl)-N<sup>3</sup>,N<sup>3</sup>dipropylisophthalamide (62 mg): mp 65-67 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.21 (br s, 1H), 8.15 (s, 2H), 7.69 (s, 1H), 7.60 (s, 1H), 7.25 (t, J = 8 Hz, 1H), 7.19-7.17 (m, 3H), 7.10 (d, J = 8Hz, 1H), 6.96 (d, J = 8 Hz, 2H), 6.60 (t, J = 8 Hz, 1H), 4.27(d, J = 8 Hz, 1H), 3.88-3.80 (m, 3H), 3.53 (br s, 2H), 3.44 10 (br s, 2H), 3.09-3.01 (m, 4H), 2.85-2.82 (m, 2H), 2.62 (t, J =8 Hz, 2H), 1.74 (br s, 2H), 1.45 (br s, 2H), 1.21 (t, J=8Hz, 3H), 1.03 (t, J = 7 Hz, 3H), 0.66 (t, J = 7 Hz, 3H); APCI  $MS m/z 633 [M + H]^+$ 

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#### EXAMPLE SP-281

 $N^1-\{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-N^3-methyl-5-(1,3-oxazol-2-yl)-N^3-$ 

20 propylisophthalamide

To 3-{[Methyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid (350 mg, 1.2 mmol) in DMF (5 mL) is added diisopropylethylamine (835  $\mu$ L, 4.8 mmol), HATU (554 mg, 1.5 mmol), then (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (488 mg, 1.2 mmol). The reaction is stirred for 16 h at room temperature. The reaction is

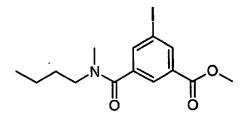
partitioned between chloroform and water. The organic layer is washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/chloroform) gives the title compound. ESI MS m/z 605.3 [M + H]<sup>+</sup>.

EXAMPLE SP-282

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Step 1

Methyl 3-{[butyl(methyl)amino]carbonyl}-5-iodobenzoate



3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and disopropylethylamine (1.7 mL, 15 9.8 mmol), HATU (1.5 g, 3.9 mmol), and N-methylbutylamine (581 μL, 4.9 mmol) are added. The reaction stirred at room temperature 2 h. The reaction is partitioned between ethyl acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried 20 (sodium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography pressure. 40% ethyl acetate/hexane) provides the title (silica, compound. ESI MS m/z 376.1 [M + H]<sup>+</sup>.

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Step 2

Methyl 3-{[butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate

To a -70 °C stirred solution of oxazole (167 mg, 2.4 mmol) in tetrahydrofuran (4 mL) is added n-butyllithium (1.6 M in hexanes, 1.7 mL, 2.7 mmol). After 30 min, zinc chloride (1 M in diethyl ether, 7.3 mL, 7.3 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a 3-{[butyl(methyl)amino]carbonyl}-5solution of methyl iodobenzoate (864 mg, 2.3 mmol) in anhydrous tetrahydrofuran (3 mL) followed by palladium(0) tetrakis(triphenylphosphine) (112 mg, 0.10 mmol). The reaction mixture is heated at reflux 10 The reaction mixture is cooled, diluted with ethyl for 1.5 h. acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title 15 compound. ESI MS m/z 317.1 [M + H]<sup>+</sup>.

Step 3
3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic
20 acid

To methyl 3-{[butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate (660 mg, 2.1 mmol) in tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium hydroxide monohydrate (175 mg, 4.2 mmol), and the reaction is

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stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS 5 m/z 301.1 [M - H].

Step 4

N¹-butyl-N³-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N¹-methyl-5-(1,3-oxazol-2-yl)isophthalamide

3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-oxazol-2yl)benzoic acid (237 mg, 0.78 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (546  $\mu$ L, 3.1 mmol), HATU (358 15 mg, 0.94 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (319 mg, 0.78 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N (aq), 20 hydrochloric acid saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 619.3 [M + 25 H]<sup>+</sup>.

EXAMPLE SP-283

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 $N^1-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-N^3-ethyl-5-(1,3-oxazol-2-yl)-N^3-propylisophthalamide$ 

## Step 1

5 Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-iodobenzoate

3-Iodo-5-(methoxycarbonyl)benzoic acid (1 g, 3.3 mmol) is dissolved in DMF (10 mL), and disopropylethylamine (1.7 mL, 9.8 mmol), HATU (1.5 g, 3.9 mmol), and N-ethylpropylamine (572 The reaction stirred at room μL, 4.9 mmol) are added. 10 The reaction is partitioned between ethyl temperature 16 h. acetate and water. The organic layer is washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography 15 pressure. (silica, 40% ethyl acetate/hexane) provides the title compound. ESI MS m/z 376.1 [M + H]<sup>+</sup>.

Step 2

20 Methyl 3-{[ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoate

To a -70 °C stirred solution of oxazole (106 mg, 1.5 mmol) in tetrahydrofuran (4 mL) is added n-butyllithium (1.6 M in hexanes, 1.0 mL, 1.7 mmol). After 30 min, zinc chloride (1 M

in diethyl ether, 4.6 mL, 4.6 mmol) is added and the reaction mixture is warmed to 0 °C for 1 h. To this mixture is added a solution of methyl 3-{[ethyl(propyl)amino]carbonyl}-5-iodobenzoate (535 mg, 1.45 mmol) in anhydrous tetrahydrofuran (1.8 mL) followed by palladium(0) tetrakis(triphenylphosphine) (120 mg, 0.10 mmol). The reaction mixture is heated at reflux for 2 h. The reaction mixture is cooled, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 60% ethyl acetate/hexane) provides the title compound. ESI MS m/z 317.1 [M + H]<sup>+</sup>.

Step 3

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3-{[Ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2-yl)benzoic acid

To methyl 3-{[ethyl(propyl)amino]carbonyl}-5-(1,3-oxazolmmol) 1.2 2-v1)benzoate (375 mg, tetrahydrofuran/methanol/water (1:1:1, 9 mL) is added lithium 20 hydroxide monohydrate (100 mg, 2.4 mmol), and the reaction is stirred at room temperature 16 h. The solution is diluted in chloroform and washed with water and saturated chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS 25 m/z 301.1 [M - H].

Step 4

 $N^{1}$ -{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}- $N^{3}$ -ethyl-5-(1,3-oxazol-2-yl)- $N^{3}$ -propylisophthalamide

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3-{[Ethyl(propyl)amino]carbonyl}-5-(1,3-oxazol-2yl)benzoic acid (290 mg, 0.96 mmol) is dissolved in DMF (5 mL), and diisopropylethylamine (668  $\mu$ L, 3.8 mmol), HATU (438 mg, 1.15 mmol), and (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (391 mg, 0.96 mmol) are added. The reaction stirred at room temperature 5 h. The reaction mixture is diluted with chloroform, washed with water, 1N saturated sodium hydrochloric acid (aq), saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 619.3 [M + H]<sup>+</sup>.

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EXAMPLE SP-284

 $N^1-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)-N^3,N^3-dipropyl-5-(1,3-thiazol-2-yl)isophthalamide$ 

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Step 1

Methyl 3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoate

To 0.5M thiazole zinc bromide (45 mL) is added methyl 3-[(dipropylamino)carbonyl]-5-iodobenzoate (8.6 g, 21.4 mmol) in THF (130 mL), then palladium(0) tetrakis(triphenylphosphine) The reaction mixture is heated at (2 q, 1.7 mmol) are added. reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS m/z 347.1  $[M + H]^{+}$ .

# 15 Step 2

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3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid

3-[(dipropylamino)carbonyl]-5-(1,3-thiazol-2-Methyl dissolved (4.4 g,12.8 mmol) is in 1:1:1 yl)benzoate tetrahydrofuran/methanol/water (60 mL), and lithium hydroxide monohydrate is added (1.1 g, 25.6 mmol), and the reaction The solution is concentrated under reduced stirred 15 min. The solution is washed pressure and diluted in chloroform. with water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 333.1 [M + H]<sup>+</sup>.

Step 3

 $N^{1}$ -((1S,2R)-1-(3,5-Difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propyl)- $N^{3}$ ,  $N^{3}$ -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide dihydrochloride

3-[(Dipropylamino)carbonyl]-5-(1,3-thiazol-2-yl)benzoic acid is dissolved in DMF (10 mL), and diisopropylethylamine (364 µL, 2.1 mmol), HATU (237 mg, 0.62 mmol), (2R,3S)-3-amino-10 4-(3,5-difluorophenyl)-1-{[3-

(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-311 (250 mg, 0.52 mmol) The reaction stirred at room temperature 4 h. are added. reaction mixture is diluted with chloroform, washed with saturated sodium bicarbonate, sodium saturated water, chloride, dried (sodium sulfate), filtered, and concentrated flash Purification by column reduced pressure. under methanol/methylene chloride) (silica, 88 chromatography provides the title compound as the free base. The residue is dissolved in diethyl ether (3 mL) and 1N hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. m/z 689.3 [M + H]<sup>+</sup>.

#### 25 EXAMPLE SP-285

Step 1

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3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid

To 0.5M thiazole zinc bromide (4.5 mL) is added methyl 3-5 { [butyl (methyl) amino] carbonyl}-5-iodobenzoate (700 mg, palladium(0) mmol) in THF (5 mL), then tetrakis(triphenylphosphine) (175 mg, 0.15 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed 10 with water, saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS m/z 333.1 [M + H]<sup>+</sup>. 15

Step 2

3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid

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3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoic acid (410 mg, 1.23 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.5 mmol), and the reaction stirred 16 h. The solution is concentrated under reduced

pressure and diluted in ethyl acetate. The solution is washed with water and saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give the title compound. ESI MS m/z 319.1 [M + H]<sup>+</sup>.

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Step 3  $N^1-Butyl-N^3-\{(1S,2R)-1-(3,5-diffluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-N^1-methyl-5-(1,3-thiazol-2-yl)isophthalamide$ 

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3-{[Butyl(methyl)amino]carbonyl}-5-(1,3-thiazol-2yl)benzoic acid (125 mg, 0.39 mmol) is dissolved in DMF (3 mL), and diisopropylethylamine (271  $\mu$ L, 1.6 mmol), HATU (178 mg, 0.47 mmol),  $(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-$ (trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride (176 mg, 0.43 mmol) are added. The reaction stirred at room The reaction mixture is diluted with temperature 4 h. chloroform, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 8% methanol/methylene chloride) provides the title compound as the free base. The residue is dissolved in diethyl ether 1N (3 mL) hydrochloric acid in diethyl ether (2 mL) is added. The mixture is concentrated under reduced pressure to yield the title compound. ESI MS m/z 635.3 [M + H]<sup>+</sup>.

EXAMPLE SP-286

Step 1

Methyl 3-{[methyl(propyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoate

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To 0.5M thiazole zinc bromide (4.1 mL) is added methyl 3iodo-5-{[methyl(propyl)amino]carbonyl}benzoate (616 mg, 1.7 (5 mL), then palladium(0) in THF mmol) tetrakis(triphenylphosphine) (158 mg, 0.14 mmol) are added. The reaction mixture is heated at reflux for 16 h, cooled to room temperature, and then filtered. The solution is washed with water, saturated sodium bicarbonate, and saturated sodium sulfate), filtered, chloride, dried (magnesium concentrated under reduced pressure. Purification by flash column chromatography (35% ethyl acetate/hexane) yields the title compound. ESI MS m/z 319.1 [M + H]<sup>+</sup>.

Step 2

N<sup>1</sup>-{(1S,2R)-1-(3,5-Difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-20 hydroxypropyl}-N<sup>3</sup>-methyl-5-(1,3-thiazol-2-yl)-N<sup>3</sup>propylisophthalamide

3-{[methyl(propyl)amino]carbonyl}-5-(1,3-thiazol-2-yl)benzoate (390 mg, 1.22 mmol) is dissolved in 1:1:1 tetrahydrofuran/methanol/water (9 mL), and lithium hydroxide monohydrate is added (103 mg, 2.4 mmol), and the reaction The solution is concentrated under reduced stirred 2 h. The residue is redissolved in DMF (5 mL), and pressure. diisopropylethylamine (355  $\mu$ L, 2.0 mmol), HATU (230 mg, 0.61 (2R, 3S) - 3 - amino - 4 - (3, 5 - difluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)] - 1 - [(3 - amino - 4 - (3, 5 - difluorophenyl)]]mmol), ethylbenzyl)amino]butan-2-ol dihydrochloride prepared by the method of EXAMPLE SP-272 (206 mg, 0.51 mmol) are added. 10 reaction stirred at room temperature 16 h. mixture is diluted with ethyl acetate, washed with water, saturated sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography pressure. 15 (silica, 9% methanol/methylene chloride) provides the title compound. ESI MS m/z 621.3 [M + H]<sup>+</sup>.

### EXAMPLE SP-287

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- {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-dipropyl-5-pyridin-4-ylisophthalamide dihydrochloride
- 25 Step 1: To a stirred solution of borate ester methyl 3[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1yl)benzoate dissolved in 1,4-dioxane (9.3 mL) was added sodium
  carbonate (2 mL of a 2 M solution in water, 4 mmol), 4bromopyridine hydrochloride (250 mg, 1.3 mmol), and the
  30 reaction mixture was degassed for 15 min. The reaction
  mixture was flushed with argon and heated to reflux overnight.
  The reaction mixture was cooled to room temperature, diluted
  with water, extracted with ethyl acetate (3 x 50 mL), dried
  (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided methyl 3- [(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, J = 7 Hz, 2H), 8.10 (t, J = 3 Hz, 1H), 8.04 (t, J = 3 Hz, 1H), 7.97 (t, J = 3 Hz, 1H), 7.48 (d, J = 6 Hz, 2H), 3.45 (m, 2H), 3.16 (m, 2H), 2.09 (s, 3H), 1.69 (m, 2H), 1.54 (m, 2H), 0.94 (m, 3H), 0.74 (m, 3H).

- of 1-methyl 3solution stirred 2:  $\mathbf{T}$ o Step [(dipropylamino)carbonyl]-5-pyridin-4-ylbenzoate (240 mg, 10 mmol) in methanol (1.5 mL), tetrahydrofuran (0.7 mL), water (0.7 mL) was added lithium hydroxide (58 mg, 1.4 mmol). The reaction mixture was stirred for 4 h, and concentrated under reduced pressure. The residue was dissolved in water, and extracted with ethyl acetate (3  $\times$  75 mL). The aqueous 15 layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with chloroform (4  $\times$  50 mL). The combined organic extracts were dried (magnesium sulfate), filtered, concentrated under reduced pressure to provide a pyridine (160 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.79 (d, J = 5 Hz, 2H), 8.45 (s, 20 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.69 (d, J = 6 Hz, 2H), 3.50 (d, J = 7 Hz, 2H), 1.74 (d, J = 7 Hz, 2H), 1.02 (m, 3H), 0.78(m, 3H).
- Step 3: To a stirred solution of pyridine from step 3 (160 mg, 0.49 mmol) in dichloromethane (1.96 mL) was added DIPEA (190 mg, 1.47 mmol), HATU (278 mg, 0.73 mmol), and HOBt (99 mg, 0.73 mmol), followed by amine 2 (200 mg, 0.49 mmol). The reaction mixture was stirred overnight at room temperature.

  The reaction mixture was partitioned between dichloromethane and water. The organic layer was washed with saturated sodium bicarbonate, saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The resulting oil was dissolved in a minimal amount of

methanol, and precipitated with hydrochloric acid (10 mL of a 1 M solution in diethyl ether, 10 mmol). The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the title compound (100 mg): mp 166-169 °C; APCI MS m/z 643  $[M + H]^+$ .

# EXAMPLE SP-288

N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-0 hydroxypropyl}-4-[(methylsulfonyl)methyl]piperidine-1carboxamide:

Step 1: To an ice-cold, stirred solution of acid 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.4 mmol) in tetrahydrofuran (11 mL) was added borane-dimethylsulfide complex (3.4 mL of a 2.0 M solution in tetrahydrofuran, 6.8 mmol). After 2 h, the reaction mixture was quenched with methanol, and concentrated under reduced pressure to provide an alcohol (939 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) & 4.11 (br s, 2H), 3.50 (t, J = 6 Hz, 2H), 2.68 (d, J = 12 Hz, 2H), 1.74-1.65 (m, 3H), 1.45 (s, 9H), 1.31 (t, J = 7 Hz, 1H), 1.14 (dd, J = 12, 4 Hz, 2H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (450 mg, 2.1 mmol) and triethylamine (0.32 mL, 2.3 25 mmol) in tetrahydrofuran (6 mL) was added methanesulfonyl The reaction mixture was chloride (0.18 mL, 2.3 mmol). stirred for 5 min and then sodium iodide (375 mg, 2.3 mmol) The reaction mixture was warmed to added. temperature and filtered. To the collected filtrate was added 30 sodium thiomethoxide (161 mg, 2.3 mmol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, and saturated sodium chloride, dried

(sodium sulfate), filtered, and concentrated under reduced pressure to provide tert-butyl 4- [(methylthio)methyl]piperidine-1-carboxylate (430 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.11 (t, J = 7 Hz, 2H), 2.69 (t, J = 12 Hz, 2H), 2.42 (d, J = 7 Hz, 2H), 2.10 (s, 3H), 1.83-1.78 (m, 2H), 1.66-1.59 (m, 2H), 1.45 (s, 9H), 1.26-1.06 (m, 2H).

Step 3: A solution of sulfide from step 2 (420 mg, 1.7 mmol), hydrogen peroxide (11 mL of a 30% solution in water, 170 mmol), and sodium bicarbonate (143 mg, 1.7 mmol) in acetone (10 mL) was stirred for 18 h. The reaction mixture was washed with 1.3 N sodium hydroxide, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to provide a sulfone (390 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) [ 4.11 (t, J = 7 Hz, 2H), 2.94 (s, 3H), 2.81-2.73 (m, 2H), 2.35-2.20 (m, 2H), 1.96-1.91 (m, 2H), 1.45 (s, 9H), 1.38-1.23 (m, 3H).

Step 4: A solution of sulfone from step 3 (390 mg, 1.4 mmol) and hydrochloric acid (4 mL of a 4 M solution in dioxane, 14 20 mmol) was stirred for 18 h. The resulting precipitate was provide tert-butyl filtration to collected by [(methylsulfonyl)methyl]piperidine-1-carboxylate (220 mg): <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.94 (br s, 1H), 8.70 (br s, 1H), 3.24-3.15 (m, 4H), 3.00 (s, 3H), 2.89 (q, J = 7 Hz, 2H), 2.29-25 2.18 (m, 1H), 1.97 (d, J = 13 Hz, 2H), 1.57-1.43 (m, 2H).

Step 5: To an ice-cold, stirred solution of triphosgene (108 mg, 0.36 mmol) and diisopropylethylamine (0.6 mL, 3.3 mmol) in methylene chloride (2.0 mL) was added amino sulfone from step 4 (210 mg, 0.98 mmol) in methylene chloride (3.5 mL) dropwise. After 5 min a solution of dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (401 mg, 0.98 mmol) was added and the reaction mixture was warmed

until the solution became homogeneous. The reaction mixture washed with 1 N was diluted with methylene chloride, hydrochloric acid (25 mL), saturated sodium bicarbonate (25 mL), and saturated sodium chloride, dried (magnesium sulfate), concentrated under reduced pressure. and filtered. Purification by flash column chromatography (silica, 15:85 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.3 mL of a 1.0 M solution in diethyl ether, 0.3 mmol). The resulting precipitate was collected by filtration to 10 provide the title compound (38 mg): mp 130-134 °C; APCI MS m/z $538 [M + H]^{+}$ .

#### EXAMPLE SP-289

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylsulfonyl)methyl]cyclohexane carboxamide

Step 1: To a stirred solution of dimethyl cyclohexane-1,4-20 dicarboxylate (10.2 g, 51 mmol) in a mixture of 2:1:1 tetrahydrofuran/methanol/water (52 mL) was added lithium hydroxide (2.13 g, 51 mmol). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was partitioned between 25 diethyl ether and water. The aqueous layer was acidified to pH 4 with 1 N hydrochloric acid, and the precipitate dried under vacuum to afford collected, and (methoxycarbonyl)cyclohexanecarboxylic acid (7.4 g): 1H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.68 (s, 3H), 2.33-2.27 (m, 2H), 2.11-2.06 30 (m, 4H), 1.50-1.43 (m, 4H).

Step 2: To an ice-cold, stirred solution of acid (3.2 g, 17 mmol) in tetrahydrofuran (40 mL) was added borane-dimethyl

sulfide complex (12 mL, 22 mmol). The reaction mixture was heated at 70 °C for 2 h and a 1:1 mixture of acetic acid/water (10 mL) added. The resulting mixture was concentrated. Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) provided methyl 4 (hydroxymethyl)cyclohexanecarboxylate (1.26 g):  $^1\!H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.67 (s, 3H), 3.48-3.46 (m, 2H), 2.26-2.15 (m, 1H), 2.05-1.85 (m, 4H), 1.52-1.42 (m, 3H), 1.02-0.97 (m, 2H).

10 Step 3: To an ice-cold, stirred solution of the alcohol (365 mg, 2.12 mmol) and triethylamine (440 μL, 4.8 mmol) in methylene chloride (5 mL) was added mesyl chloride (200 μL, 2.6 mmol). The reaction mixture was stirred for 20 min and then partitioned between methylene chloride and water. The organic layer was washed with 1 M hydrochloric acid, and saturated sodium bicarbonate, dried (magnesium sulfate), and concentrated under reduced pressure to afford a the desired mesylate, which was carried on without purification or characterization.

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Step 4: To a stirred solution of the mesylate from step 3 (2.12 mmol) in tetrahydrofuran (5 mL) was added sodium iodide (640 mg, 4.3 mmol). The reaction mixture was heated to  $60 \, ^{\circ}\text{C}$  for 5 h and then filtered. The reaction mixture was concentrated under reduced pressure, and carried on without purification or characterization.

Step 5: To a stirred solution of the iodide from step 4 (2.12 mmol) in a mixture of N,N-dimethylformamide (10 mL) and tetrahydrofuran (1 mL) was added sodium thiomethoxide (450 mg, 6.4 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction mixture was allowed to cool to room temperature, the solvents were removed, and the residue was partitioned between ether and water. The aqueous layer was acidified to

pH 1 with 1 N hydrochloric acid, extracted with ethyl acetate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford methyl 4- [(methylthio)methyl]cyclohexanecarboxylate (230 mg):  $^{1}$ H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  2.40-2.37 (m, 2H), 2.22-2.05 (m, 1H), 2.05 (s, 3H), 2.02-1.93 (m, 4H), 1.48-1.38 (m, 3H), 1.03-0.95 (m, 2H).

Step 6: To a stirred solution of the methyl sulfide (240 mg, in sodium hydroxide solution (3.5 mL, 0.5 M 10 solution) was added sodium bicarbonate (870 mg, 10.3 mmol) and acetone (1 mL) followed by the addition of a solution of oxone (1.0 g, 1.7 mmol) in 0.0004 M EDTA (4 mL). mixture was stirred at room temperature for 2 h and then quenched with sodium bisulfite. The reaction mixture was 15 acidified with hydrochloric acid and extracted with ethyl acetate (3  $\times$  100 mL). The combined organic layers were washed with water, dried (sodium sulfate), filtered, and concentrated to provide acid reduced pressure under [(methylthio)methyl]cyclohexanecarboxylic acid (240 mg): <sup>1</sup>H NMR 20 (300 MHz, CD<sub>3</sub>OD)  $\delta$  3.06-3.04 (m, 2H), 2.96 (s, 3H), 2.28-2.20 (m, 1H), 2.08-1.98 (m, 5H), 1.50-1.40 (m, 2H), 1.21-1.16 (m, 2H).

25 Step 7: To a stirred solution of the acid (120 mg, 0.6 mmol), (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (230 mg, 0.6 mmol), and HATU (210 mg, 0.6 mmol) in methylene chloride (5 mL) was added N,N-diisopropylethylamine (340 μL, 1.93 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford a crude oil. Purification by flash column

chromatography (silica, gradient 95:5 to 93:7 methylene chloride/methanol) provided the title compound (35 mg): mp 178-180 °C; ESI MS m/z 537 [M + H]<sup>+</sup>.

#### 5 EXAMPLE SP-290

 $N-\{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-5-piperidin-4-yl-N\(u)3\(d),N\(u)3\(d)-dipropylisophthalamide$ 

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Step 1: To a -70 °C stirred solution of N-Boc-piperidone (500 mg, 2.5 mmol) in tetrahydrofuran (11 mL) was added lithium 2 M solution οf а (1.37) $\mathfrak{mL}$ diisopropylamine tetrahydrofuran, 2.75 mmol). The reaction mixture was stirred for 2 h, warmed to 0  $^{\circ}$ C, and N-phenyltriflamide (955 mg, 2.67 15 The solution was allowed to warm to room. mmol) was added. temperature and was stirred for 12 h. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (3:1 hexanes/ethyl acetate) 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-20 tert-butyl dihydropyridine-1(2H)-carboxylate (240 mg):  $^{1}$ H NMR (300 MHz,  $CDCl_3$ )  $\delta 5.77$  (s, 1H), 4.05 (m, 2H), 3.63 (m, 2H), 2.45 (m, 2H), 1.48 (s, 9H).

25 Step 2: To a stirred solution of the triflate (240 mg, 0.72 mmol) and borate ester methyl 3-[(dipropylamino)carbonyl]-5-(3,3,4,4-tetramethylborolan-1-yl)benzoate (280 mg, 0.72 mmol) in dioxane (3 mL) was added sodium carbonate (1.1 mL of a 2 M solution in water, 2.16 mmol). The reaction mixture was flushed with argon, palladium(0) tetrakis(triphenylphosphine) (34 mg, 0.03 mmol) was added, and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth, dried (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (90:10 chloroform/methanol) afforded an acid (160 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 8.11 (s, 1H), 7.95 (s, 1H), 7.58 (s, 1H), 6.15 (br s, 1H), 4.10 (s, 2H), 3.65 (m, 2H), 3.48 (m, 2H), 3.16 (s, 2H), 2.54 (s, 2H), 1.70 (s, 2H), 1.50 (s, 9H), 1.25 (m, 2H), 0.99 (s, 3H), 0.76 (s, 3H).

Step 3: A solution of the acid from step 2 (160 mg, 0.37 mmol) and 10% Pd/C (25 mg) in ethanol (10 mL) was degassed with nitrogen for 15 min, and shaken under an atmosphere of hydrogen at 50 psi for 12 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to give acid 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-5-

[(dipropylamino)carbonyl]benzoic acid (121 mg), which was carried on without further purification:  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 7.94 (d, J = 12 Hz, 2H), 7.44 (s, 1H), 4.27 (br s, 2H), 3.43 (m, 2H), 3.14 (m, 2H), 2.78 (m, 4H), 1.84 (m, 3H), 1.63 (m, 6H), 1.49 (s, 9H), 1.23 (m, 3H), 0.86 (m, 3H), 0.75 (m, 20 3H).

Step 4: To a stirred solution of the acid (120 mg, 0.28 mmol) was added methylene chloride (2 mL) diisopropylethylamine (0.141 mL, 0.84 mmol), HOBt (56 mg, 0.42 mmol), and HATU (160 mg, 0.42 mmol), followed by (2R,3S)-3amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2ol (114 mg, 0.28 mmol). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with methylene chloride (25 mL), washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography (93:7 chloroform/methanol) afforded a piperidine (90 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 7.61 (s, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.14 (m,

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4H), 6.79 (m, 2H), 6.64 (m, 1H), 4.29 (m, 3H), 3.68 (m, 4H), 3.47 (m, 2H), 3.02 (m, 4H), 2.77 (m, 5H), 2.66 (m, 2H), 1.71 (m, 8H), 1.48 (s, 9H), 1.24 (m, 5H), 0.99 (m, 3H), 0.73 (m, 3H).

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Step 5: A solution of piperidine from step 4 (90 mg, 0.12 mmol) and hydrochloric acid (0.3 mL of a 4.0 M solution in dioxane, 1.2 mmol) was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure, washed with ether (50 mL), and filtered. Purification by flash column chromatography (89:10:1 chloroform/methanol/ammonium hydroxide) afforded the title compound (35 mg): mp 84-87 °C; ESI MS m/z 649 [M + H]\*.

# 15 EXAMPLE SP-291

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(1,3-oxazol-2-yl)benzamide hydrochloride

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stirred solution of acid Step 1: To an ice-cold, (methoxycarbonyl)-5-nitrobenzoic acid (24.6 g, 0.11 mol) tetrahydrofuran (200 mL) was added borane-dimethylsulfide complex (82 mL of a 2.0 M solution in tetrahydrofuran, 0.16 mol) and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, quenched with methanol, and the solvent was removed under reduced column pressure. Purification by flash chromatography (silica, 1:1 ethyl acetate/hexanes) provided an alcohol (16 g): <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta 8.51$  (d, J = 1 Hz, 1H), 8.42 (s, 1H), 8.32 (s, 1H), 5.69 (t, J = 6 Hz, 1H), 4.70 (d, J = 6 Hz, 2H), 3.93 (s, 3H).

Step 2: To an ice-cold, stirred solution of the alcohol from step 1 (6.6 g, 32 mmol) in methylene chloride was added phosphorus tribromide (1.5 mL, 16 mmol) and the reaction mixture was stirred for 40 min. The reaction mixture was diluted with methylene chloride, washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure to give a bromide (8.1 g):  $^{1}$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.79 (t, J = 2 Hz, 1H), 8.45 (t, J = 2 Hz, 1H), 8.39 (d, J = 2 Hz, 1H), 4.57 (s, 2H), 4.00 (s, 3H).

Step 3: A solution of bromide from step 2 (8.1 g, 32 mmol) and 10% Pd/C (1.0 g) in 13:4:1 methanol/ethyl acetate/acetic acid (90 mL) was shaken under an atmosphere of hydrogen at 45 psi for 24 h. The reaction mixture was filtered through diatomaceous earth, and concentrated under reduced pressure to provide 1 methyl 3-amino-5-methylbenzoate (2.8 g): ESI MS m/z 166 [M + H]<sup>+</sup>.

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20 Step 4: To an ice-cold, stirred solution of the aniline (2.8 g, 17 mmol) in 2 N hydrochloric acid (48 mL) was added a solution of sodium nitrite (1.2 g, 17 mmol) in water (10 mL), and the reaction mixture was stirred for 30 min. reaction mixture was added to an ice-cold, stirred solution of 25 potassium iodide (5.6 g, 34 mmol) and copper(I) iodide (1.6 g, 8.6 mmol) in water (10 mL). The reaction mixture was warmed to room temperature over 2 h and then diluted with ethyl acetate. The organic layer was washed with a 10% solution of sodium thiosulfate, and saturated sodium chloride, 30 (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography (silica, 1:9 ethyl acetate/hexanes) provided an iodide (1.4 g):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.16 (s, 1H), 7.80 (d, J = 1 Hz, 1H), 7.72 (d, J = 1 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H).

Step 5: To a -70 °C stirred solution of oxazole (174 mg, 2.5 mmol) in tetrahydrofuran (5 mL) was added n-butyllithium (1.7 mL of a 1.6 M solution in hexanes, 2.8 mmol). After 30 min, zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 5 mmol) was added and the reaction mixture was warmed to 0 °C for To this mixture was then added iodide from step 4 (695 2.5 followed by mg, mmol) palladium(0) (triphenylphosphine) (145 mg, 0.13 mmol). The reaction 10 mixture was heated at reflux for 16 h. The reaction mixture was cooled, and diluted with ethyl acetate (50 mL). organic layer was washed with water, and saturated sodium filtered, chloride, dried (magnesium sulfate), concentrated under reduced pressure. Purification by flash 1:1 ethyl acetate/hexanes) 15 column chromatography (silica, provided an oxazole (330 mg):  $^{1}H$  NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  8.45 (s, 1H), 8.08 (d, J = 1 Hz, 1H), 8.01 (s, 1H), 7.97 (d, J = 1)Hz, 1H), 7.32 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H); ESI MS m/z $218 [M + H]^+$ .

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Step 6: To a stirred solution of the ester from step 5 (384 mg, 1.7 mmol) in methanol (5 mL) was added potassium hydroxide (15 mL of a 1.0 M solution in water, 15 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an acid (358 mg):  $^{1}$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.2 (br s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.42 (s, 1H), 2.45 (s, 3H).

Step 7: A solution of the acid from step 6 (358 mg, 1.8 mmol), HATU (1.0 g, 2.6 mmol), HOBt (357 mg, 2.6 mmol), diisopropylethylamine (500 µL, 2.6 mmol) was stirred in methylene chloride (2.0 mL) for 15 min. A solution of dihydrochloride of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (718 mg, 1.8 mmol) and diisopropylethylamine (500 µL, 2.6 mmol) in methylene chloride (2.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with methylene chloride, washed with 1 N hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium chloride, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. solid was dissolved in methanol (2 mL), and treated with hydrochloric acid (0.5 mL of a 1.0 M solution in diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide the title compound (250 mg): mp 105-107 °C; APCI MS m/z 520 [M + H]<sup>+</sup>.

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#### EXAMPLE SP-292

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(methylsulfonyl)methyl]thiophene-2-

25 carboxamide

Step 1: To a solution of acid 5-(methoxycarbonyl)thiophene-2-carboxylic acid (1.00 g, 5.37 mmol) in tetrahydrofuran (21.5 mL) was added borane-dimethylsulfide complex (3.0 mL of a 2.0 M soltion in tetrahydrofuran, 6.00 mmol). The reaction mixture was heated at reflux for 24 h and then carefully quenched with anhydrous methanol (1.0 mL) and cooled to room temperature. The reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The

combined organic phases were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated to yield the desired alcohol (820 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (d, J = 4 Hz, 1H), 6.96 (d, J = 4 Hz, 1H), 4.83 (s, 2H), 3.87 (s, 3H).

Step 2: To a 0 °C solution of the alcohol prepared in step 1 (805 mg, 4.67) in tetrahydrofuran (31 mL) containing triethylamine (790 µL, 5.61 mmol) and dimethylaminopyridine (6 mg) was added methanesulfonyl chloride (400 µL, 5.14 mmol) and the reaction mixture was stirred for 0.5 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to provide the crude mesylate, which was used in the next step without further purification: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (m, 1H), 7.18 (m, 1H), 5.39 (s, 2H), 3.90 (s, 3H), 2.97 (s, 3H).

- To the mesylate prepared in step 2 in N, N-Step 3: dimethylformamide (10 mL) was added sodium thiomethoxide (516 mg, 7.0 mmol) and the reaction mixture was warmed to 50 °C for 20 The reaction was diluted with water (200 mL) and 18 h. extracted with chloroform (4 x 25 mL). The combined organic phases were washed with 5% lithium chloride, water, saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give the desired 25 sulfide (760 mg) which was used without further purification:  $^{1}\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.64 (d, J = 4 Hz, 1H), 6.93 (d, J = 4 Hz, 1H), 3.89 (m, 5H), 2.08 (s, 3H).
- 30 Step 4: To a 0 °C solution of the sulfide prepared in step 3 (760 mg, 3.75 mmol) in chloroform (6.25 mL) was added 70% m-CPBA (2.31 g, 9.37 mmol) and the reaction stirred at 0 °C for 2.5 h. The reaction mixture was then diluted with chloroform and washed with 1 N sodium hydroxide, water, and saturated

sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the desired sulfone (780 mg) which was used without further purification:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.74 (d, J = 4 Hz, 1H), 7.20 (d, J = 4 Hz, 1H), 4.46 (s, 2H), 3.89 (m, 3H), 2.87 (s, 3H).

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Step 5: To a solution of the sulfone prepared in step 4 (268 mg, 1.14 mmol) in 2:1:1 dioxane/methanol/water (7.6 mL) was added lithium hydroxide monohydrate (53 mg, 1.14 mmol) and the reaction mixture was stirred for 24 h at room temperature. 10 The reaction mixture was concentrated under reduced pressure and the solid residue was partitioned between ethyl acetate and water. The aqueous phase was acidified with 1 N hydrochloric acid and extracted several times with diethyl 15 ether. The combined ether extracts were washed with water, sodium chloride, dried and saturated (sodium sulfate), filtered, and concentrated under reduced pressure to provide 5-[(methylsulfonyl)methyl]thiophene-2-carboxylic acid (115 mg) which was used without further purification: 1H NMR (300 MHz, 20 CDCl<sub>3</sub>)  $\delta$  7.73 (d, J = 4 Hz, 1H), 7.20 (d, J = 4 Hz, 1H), 4.52 (s, 2H), 2.90 (s, 3H); ESI MS (negative mode) m/z 219 [M - H].

Step 6: To a solution of acid from step 5 (115 mg, 0.52 mmol) and N,N-diisopropylethylamine (540 µL, 3.12 mmol) in methylene chloride (6.5 mL) was added HBTU (200 mg, 0.52 mmol) and the reaction mixture was stirred for 0.5 h. (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (211 mg, 0.52 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by flash chromatography

(silica, 1-5% methanol in chloroform) gave the title compound (45 mg): mp 128-131 °C;; ESI MS m/z 537 [M + H]<sup>+</sup>.

# EXAMPLE SP-293

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 $N-\{(1S,2R)-1-(3,5-diffluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1\}-3-methyl-5-(1,3-thiazol-2-y1)benzamide hydrochloride$ 

Step 1: To a -70 °C stirred solution of thiazole (214 mg, 2.5 10 mmol) in tetrahydrofuran (5 mL) was added n-butyllithium (1.7 mL of a 1.6 M solution in hexanes, 2.8 mmol). After 30 min, zinc chloride (7.5 mL of a 1 M solution in diethyl ether, 7.5 mmol) was added and the reaction mixture was warmed to 0 °C for To this mixture was then added iodide described above 15 1 h. 2.5 mmol) followed by palladium(0) (695 mg, (145 mg)0.13 mmol). tetrakis(triphenylphosphine) reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled and diluted with ethyl acetate (50 mL). The organic layer was washed with water, and saturated sodium 20 filtered, (magnesium sulfate), chloride, dried Purification by flash concentrated under reduced pressure. 1:1 ethyl acetate/hexanes) column chromatography (silica, provided a thiazole (208 mg):  $^{1}\text{H}$  NMR (300 MHz, CDCl $_{3}$ )  $\delta$  8.38 (s, 1H), 8.02 (d, J = 1 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 325 Hz, 1H), 7.37 (d, J = 3 Hz, 1H), 3.95 (s, 3H), 2.48 (s, 3H).

Step 2: To a stirred solution of the ester from step 1 (208 mg, 0.89 mmol) in 2:1:1 methanol/tetrahydrofuran/water (4 mL) was added lithium hydroxide (75 mg, 1.8 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The residue was diluted with water and washed with ethyl acetate. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted

with chloroform (5 x 100 mL). The combined organic extracts were dried (sodium sulfate), filtered, and concentrated under reduced pressure to give an acid (146 mg):  $^{1}$ H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  13.17 (br s, 1H), 8.28 (s, 1H), 8.01 (d, J = 1 Hz, 1H), 7.96 (d, J = 3 Hz, 1H), 7.85 (d, J = 3 Hz, 2H), 2.45 (s, 3H).

Step 3: A solution of the acid from step 2 (140 mg, 0.64 mmol), HATU (364 mg, 0.96 mmol) and disopropylethylamine (170 μL, 0.96 mmol) was stirred in methylene chloride (2.0 mL) for 10 15 min. A solution of dihydrochloride (2R,3S)-3-amino-4-(3,5difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol 0.64 mmol) and diisopropylethylamine (170  $\mu$ L, 0.96 mmol) in methylene chloride (2.0 mL) was added and the reaction mixture was stirred overnight. The reaction mixture was diluted with 15 methylene chloride, washed with 1 N hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), and saturated sodium dried sulfate), chloride, (magnesium filtered, and concentrated under reduced pressure. Purification by flash 20 column chromatography (silica, 1:9 methanol/chloroform) provided a clear solid. The solid was dissolved in methanol (1 mL), and treated with hydrochloric acid (0.5 mL of a 1.0 M solution in diethyl ether, 0.5 mmol). The resulting precipitate was collected by filtration to provide the title compound (100 mg): mp 178-180 °C; APCI MS m/z 536 [M + H]<sup>+</sup>. 25

# EXAMPLE SP-293

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-30 hydroxypropyl}-4-[(methylsulfonyl)methyl]cyclohexanecarboxamide

Step 1: To an ice-cold, stirred solution of cyclohexane-1,4-dicarboxylic acid (3.0 g, 17 mmol) in a mixture of 2:1 tetrahydrofuran/methanol (24 mL) was added trimethylsilyl diazomethane (9 mL of a 2.0 M in hexanes, 18 mmol). The reaction mixture was stirred at room temperature for 2 h. Acetic acid (5 mL) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, 10:1:0.01 hexanes/ethyl acetate/acetic acid) provided 4-(methoxycarbonyl)cyclohexanecarboxylic acid (1.00 g):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.68 (s, 3H), 2.53-2.47 (m, 2H), 1.97-1.89 (m, 4H), 1.74-1.66 (m, 4H).

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To an ice-cold, stirred solution of acid from step 1 (700 mg, 3.8 mmol) in tetrahydrofuran (10 mL) was added borane-dimethyl sulfide complex (2 mL, 4.1 mmol). The 15 reaction mixture was warmed to room temperature for 2 h and a 1:1 mixture of acetic acid/water (10 mL) was added. The resulting mixture was concentrated under reduced pressure. Purification by flash column chromatography (silica, methyl acetate) provided 20 hexanes/ethyl (hydroxymethyl)cyclohexanecarboxylate (560 mg): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  3.68 (s, 3H), 3.51-3.46 (m, 2H), 2.59-2.57 (m, 1H), 2.05-2.00 (m, 2H), 1.65-1.55 (m, 5H), 1.31-1.27 (m, 2H).

Step 3: To an ice-cold, stirred solution of alcohol from step 25 2 (300 mg, 1.8 mmol) and triethylamine (370  $\mu L,$  2.7 mmol) in methylene chloride (5 mL) was added mesyl chloride (170  $\mu$ L, 2.1 The reaction mixture was stirred for 20 min and then partitioned between methylene chloride and water. The organic layer was washed with 1 N hydrochloric acid, and saturated 30 (magnesium sulfate), and dried sodium bicarbonate, concentrated under reduced pressure to afford a the desired carried on without purification or mesylate, which was characterization.

Step 4: To a stirred solution of the mesylate from step 3 (1.8 mmol) in tetrahydrofuran (5 mL) was added sodium iodide (530 mg, 3.5 mmol). The reaction mixture was heated at 60 °C for 5 h, cooled to room temperature, and then filtered. The reaction mixture was concentrated under reduced pressure, and carried on without purification or characterization.

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Step 5: To a stirred solution of the iodide from step 4 (1.8 mmol) in a mixture of N, N-dimethylformamide (10 mL) 10 tetrahydrofuran (1 mL) was added sodium thiomethoxide (375 mg, 5.3 mmol). The reaction mixture was heated at 70 °C for 15 h. The reaction mixture was then cooled to room temperature, the solvents were removed, and the residue partitioned between ether and water. The aqueous layer was acidified to pH 1 with 15 1 N hydrochloric acid, extracted with ethyl acetate, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford 4-[(methylthio)methyl]cyclohexanecarboxylic acid (50 mg):  $^{1}$ H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  2.53-2.51 (m, 1H), 20 2.43-2.41 (m, 3H), 2.05 (s, 3H), 2.05-1.95 (m, 2H), 1.71-1.53(m, 4H), 1.36-1.30 (m, 2H).

Step 6: To a stirred solution of methyl sulfide from step5 (100 mg, 0.5 mmol) in sodium hydroxide solution (1.5 mL, 0.5 M solution in water) was added sodium bicarbonate (360 mg, 4.3 mmol) and acetone (1 mL) followed by the addition of a solution of oxone (430 mg, 0.7 mmol) in 0.0004 M EDTA (2 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with sodium bisulfite. The reaction mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water, dried (sodium sulfate), filtered, provide reduced pressure to concentrated under [(methylsulfonyl)methyl]cyclohexanecarboxylic acid (100 mg): H

NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  3.11-3.08 (m, 2H), 2.96 (s, 3H), 2.53-2.51 (m, 1H), 2.18-2.16 (m, 1H), 1.99-1.93 (m, 2H), 1.79-1.25 (m, 6H).

Step 7: To a stirred solution of acid from step 6 (100 mg, 0.5 (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3mmol), ethylbenzyl)amino]butan-2-ol (190 mg, 0.5 mmol), and HATU (175 mg, 0.5 mmol) in methylene chloride (5 mL) was added N, Ndiisopropylethylamine (280  $\mu L$ , 1.6 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction 10 mixture was partitioned between methylene chloride and water. The organic layer was washed with water, dried (sodium sulfate), filtered, and concentrated under reduced pressure to Purification by flash crude oil. 92:8 methylene gradient 95:5 to chromatography (silica, 15 chloride/methanol) provided the title compound (60 mg): mp 45-50 °C; ESI MS m/z 537 [M + H]<sup>+</sup>.

# EXAMPLE SP-293

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperidin-3-yl-N,N-dipropylisophthalamidehydrochloride

Step 1: To a stirred solution of 3-bromo-pyridine (205 mg, 1.3 25 3-[(dipropylamino)carbonyl]-5-(3,3,4,4methyl mmol) and tetramethylborolan-1-yl)benzoate (500 mg, 1.3 mmol) in dioxane (9 mL) was added sodium carbonate (2.0 mL of a 2 M solution in The reaction mixture was flushed with water, 3.9 mmol). argon, palladium(0) tetrakis(triphenylphosphine) (36 mg, 0.052 30 mmol) was added and the reaction mixture was heated at reflux The reaction mixture was cooled to for 12 h. through diatomaceous earth, dried filtered temperature, (magnesium sulfate), filtered, and concentrated under reduced

pressure. Purification by flash column chromatography (3:2 hexanes/ethyl acetate) afforded a pyridine (200 mg):  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.88 (m, 1H), 8.65 (m, 1H), 8.31 (m, 1H), 8.07 (m, 1H), 7.92 (m, 1H), 7.79 (m, 1H), 7.67 (m, 1H), 3.98 (m, 3H), 3.50 (m, 2H), 3.21 (m, 2H), 1.66 (m, 4H), 1.07 (m, 3H), 0.78 (m, 3H).

Step 2: A solution of the pyridine from step 1 (160 mg, 0.37 mmol) and platinum oxide (15 mg) in ethanol (2.5 mL), water (0.5 mL), and concentrated hydrochloric acid (1.0 mL) was 10 degassed with nitrogen for 15 min, and shaken under an The reaction atmosphere of hydrogen at 50 psi for 12 h. earth and through diatomaceous mixture was filtered concentrated under reduced pressure to afford methyl 3-[(dipropylamino)carbonyl]-5-piperidin-3-ylbenzoate (204 15 quantitative), which was carried forward without further purification:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 9.62 (m, 3H), 8.02 (m, 3H), 4.78 (m, 2H), 3.96 (s, 3H), 3.61 (m, 5H), 2.04 (m, 5H), 1.34 (m, 3H), 0.91 (m, 6H).

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Step 3: To a stirred solution of piperidine from step 2 (204 mg, 0.59 mmol) in methylene chloride (1.6 mL) was added Boc anhydride (162 mg, 0.65 mmol) and triethylamine (0.122 mL, 0.88 mmol). The solution was stirred at room temperature for 2 d. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded a Boc-protected piperidine (100 mg): ¹H NMR (300 MHz, CDC1<sub>3</sub>) δ7.93 (t, J = 3 Hz, 1H), 7.88 (t, J = 3 Hz, 1H), 7.42 (t, J = 3 Hz, 1H), 4.16 (m, 2H), 3.93 (s, 3H), 3.46 (m, 2H), 3.13 (m, 2H), 2.78 (m, 3H), 2.03 (d, J = 10 Hz, 1H), 1.70 (m, 7H), 1.48 (m, 9H), 1.00 (m, 3H), 0.75 (m, 3H).

Step 4: To a stirred solution of piperidine from step 3 (100 mg, 0.22 mmol) in methanol (2 mL) was added potassium

hydroxide (2.2 mL of a 1 M solution in water, 2.2 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was acidified to pH 4-5 with 1 N hydrochloric acid and extracted with chloroform (5 x 50 mL). The combined organic layers were dried (magnesium sulfate), filtered, and concentrated under reduced pressure to afford an acid (90 mg)1: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 87.99 (s, 1H), 7.94 (s, 1H), 7.47 (s, 1H), 4.12 (m, 2H), 3.47 (m, 2H), 3.14 (m, 2H), 2.77 (m, 3H), 2.03 (m, 1H), 1.67 (m, 7H), 1.48 (s, 9H), 0.98 (m, 3H), 0.77 (m, 3H).

Step 5: To a stirred solution of piperidine from step 4 (90 mg, 0.21 mmol) in methylene chloride (1 mL) was added N, Ndiisopropylethylamine (0.142 mL, 0.84 mmol), HOBt (42 mg, 0.31 15 mmol), and HATU (118 mg, 0.31 mmol) followed by (2R,3S)-3amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-The reaction was stirred for 16 h at ol (86 mg, 0.21 mmol). The reaction mixture was diluted with room temperature. methylene chloride (25 mL), washed with water, saturated 20 sodium bicarbonate, and saturated sodium chloride, (magnesium sulfate), filtered, and concentrated under reduced Purification by flash column chromatography (95:5 pressure. chloroform/methanol) afforded a piperidine (100 mg) which was carried forward without further characterization. 25

Step 6: A solution of piperidine from step 5 (100 mg, 0.15 mmol) and hydrochloric acid (0.4 mL of a 4.0 M solution in dioxane, 1.5 mmol) was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure and washed with ether (50 mL). The precipitate that formed was collected by filtration to give the title compound (60 mg): mp 145-145 °C; ESI MS m/z 649  $[M + H]^+$ .

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EXAMPLE SP-294

1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-1H-pyrrole-2-carboxamide

Step 1: To a stirred solution of ethanol (54 mL) was added sodium metal (1.29 g, 54.00 mmol). The reaction mixture was stirred for 1 h and then diethyl acetamidomaloante (2.37 g, 10 10.92 mmol) was added. The reaction mixture was heated at reflux for 1 h and 1,4-dichloro-2-butyne (1.14 mL, 11.64 mmol) was added. The reaction mixture was refluxed for 1 h, cooled to room temperature, and concentrated under reduced pressure. The resulting residue was partitioned between ethyl acetate 15 and water. The organic layer was washed with saturated sodium chloride, dried (sodium sulfate), treated with activated earth, through diatomaceous filtered charcoal, concentrated under reduced pressure to yield ethyl 5-methyl-1H-pyrrole-2-carboxylate (1.26 g):  $^1\text{H}$  NMR (300 MHz, CDCl3)  $\delta$ 20 8.82 (br s, 1H), 6.81 (s, 1H), 5.95 (s, 1H), 4.31 (q, J = 6Hz, 2H), 2.31 (s, 3H), 1.34 (t, J = 6 Hz, 3H).

Step 2: A mixture of pyrrole from step 1 (240 mg, 1.71 mmol), potassium carbonate (306 mg, 2.21 mmol), and butyl bromide (328 mg, 2.39 mmol) in acetonitrile (10 mL) was heated to 40 °C for 2 d. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a brown oil. Purification by flash column chromatography (silica, 5.5:1 hexanes/ethyl acetate) gave an ester (232 mg):  $^1$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  6.91 (d, J = 3 Hz, 1H), 5.88 (d, J = 3 Hz, 1H), 4.24

(m, 4H), 2.26 (s, 3H), 1.65 (m, 2H), 1.37 (m, 5H), 0.99 (m, 3H); ESI MS m/z 210  $[M + H]^+$ .

Step 3: A mixture of the ester from step 2 (232 mg, 1.11 mmol) and 3:1:1 methanol/tetrahydrofuran/2 N sodium hydroxide (5 mL) was stirred overnight. The reaction was not complete after 24 The reaction mixture was heated to 40 °C for 4 h, cooled to room temperature, and then partitioned between ethyl acetate The aqueous layer was acidified to pH 3 with 1 N and water. hydrochloric acid and extracted with chloroform. The organic 10 layer was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give 1-butyl-5-methyl-1H-pyrrole-2carboxylic acid (110 mg):  $^{1}\text{H}$  NMR (300 MHz, CDCl3)  $\delta$  7.04 (d, J= 3 Hz, 1H), 5.93 (d, J = 3 Hz, 1H), 4.24 (m, 2H), 2.28 (s, ...3H), 1.67 (m, 2H), 1.43 (m, 2H), 0.99 (m, 3H). 15

Step 4: To a stirred solution of (2R,3S)-3-amino-4-(3,5difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (248 0.608 mmol), acid (110 mg, 0.608 mmol), HOBt (82 mg, 0.608 mmol), and N-methylmorpholine (99 mg, 2.43 mmol) in methylene chloride (5 mL) was added EDC (210 mg, 1.09 mmol). reaction mixture was stirred overnight and then partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, Purification by and concentrated under reduced pressure. column chromatography (silica, 9:1 methylene flash chloride/methanol) gave the title compound (100 mg): mp 116-121 °C; ESI MS m/z 498 [M + H]<sup>+</sup>.

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# EXAMPLE SP-295

N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-ylmethyl)amino]propyl}-5-methyl-N,N-dipropylisophthalamide

1: A mixture of tert-butyl (1S,2R)-3-amino-1-(3,5difluorobenzyl)-2-hydroxypropylcarbamate (170 mg, 0.538 mmol), 0.538 mmol), 1H-pyrrole-2-carbaldehyde (51 mg, triethylamine (60 mg, 0.592 mmol) was stirred in chloroform (10 mL) containing magnesium sulfate for 4 h. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was dissolved in 2-propanol (10 mL) and sodium borohydride (26 mg, 0.699 mmol) was added. reaction mixture was stirred overnight and then treated with 10 The reaction mixture was concentrated under reduced methanol. Purification by flash column chromatography pressure. (silica, 9:1 chloroform/methanol) gave tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-

- 15 ylmethyl)amino]propylcarbamate (132 mg):  $^{1}$ H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  6.82 (m, 4H), 6.21 (s, 1H), 6.09 (m, 1H), 4.09 (s, 2H), 3.66 (m, 2H), 3.19 (m, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.88 (m, 1H), 1.31 (s, 9H).
- 20 Step 2: To a stirred solution of the pyrrole from step 1 (132 mg, 0.334 mmol) in dioxane (3 mL) was added hydrochloric acid (0.33 mL, 4 N dioxane, 1.34 mmol). The reaction mixture was stirred overnight and then concentrated under reduced pressure to give an amine (134 mg, quantitative) as a brown solid, which was used without any further characterization or purification.
- Step 3: To a stirred mixture of the amine from step 2 (134 mg, 0.334 mmol), 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid (88 mg, 0.334 mmol), HOBt (45 mg, 0.334 mmol), and N-methylmorpholine (203 mg, 2.00 mmol) in methylene chloride (5 mL) was added EDC (115 mg, 0.601 mmol). After 24 h, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with 1 N hydrochloric

acid, saturated sodium bicarbonate, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a white solid. Purification by flash column chromatography (silica, 9:1:1 methylene chloride/methanol/ammonium hydroxide) gave the title compound (27 mg): mp 63-74 °C; ESI MS m/z 541 [M + H]<sup>+</sup>.

# EXAMPLE SP-296

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10 N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperazin-1-yl-N,N-dipropylisophthalamidehydrochloride

In a sealed tube, a solution of dimethyl 1: Step bromoisophthalate (5.0 g, 18.3 mmol), N-benzylpiperazine (4.0 15 mL, 23.0 mmol), and cesium carbonate (8.4 g, 25.7 mmol) in toluene (36 mL) was degassed with nitrogen at room temperature for 20 minutes. Palladium (II) acetate (225 mg, 0.92 mmol) and BINAP (1.7 g, 2.74 mmol) were quickly added under nitrogen and the solution heated to 80 °C overnight to yield a yellow 20 The reaction mixture was solution with a white suspension. cooled to room temperature, vacuum filtered, and the solid rinsed with fresh toluene. The filtrate was then concentrated under reduced pressure to yield a yellow oil. Purification by flash chromatography (silica, 80:20 hexanes/ethyl acetate) 25 desired dimethyl 5-(4-benzylpiperazin-1the gave yl)isophthalate (4.40 g): ESI MS m/z 369  $[M + H]^+$ .

Step 2: To a solution of the ester from step 1 (1.0 g, 2.70 mmol) in 2:1:1 dioxane/methanol/water (18 mL) was added lithium hydroxide monohydrate (100 mg, 2.44 mmol) and the reaction mixture stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the solid residue partitioned between ethyl acetate and water.

The organic layer was set aside and the aqueous phase acidified with 1 N hydrochloric acid and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide the desire monoacid (945 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.50-10.30 (br s, 1H), 8.19-8.12 (m, 1H), 7.80-7.60 (m, 2H), 7.35-7.26 (m, 5H), 3.91 (s, 3H), 3.73 (s, 2H), 3.36-3.33 (m, 4H), 2.77-2.71 (m, 4H); ESI MS m/z 355 [M + H]<sup>+</sup>.

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Step 3: To a solution of the monoacid prepared in step 2 (1.2 g, 3.38 mmol) in methylene chloride (22.5 mL) was added triethylamine (940 μL, 6.76 mmol), N.N-dipropylamine (554 μL, 4.0 mmol), and 2-chloro-1-methylpyridinium iodide (865 mg, 15 3.38 mmol). The reaction mixture was stirred at room temperature overnight. The residue was then diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a yellow oil. Purification by flash 20 column chromatography (silica, 80:20 hexanes/ethyl acetate) gave the desired amide (1.0 g):  $^{1}H$  NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.59-7.58 (m, 1H), 7.44-7.42 (m, 1H), 7.35-7.26 (m, 5H), 7.05-7.04(m, 1H), 3.89 (s, 3H), 3.56 (s, 2H), 3.50-3.35 (m, 2H), 3.28-3.25 (m, 4H), 3.20-3.05 (m, 2H), 2.62-2.58 (m, 4H), 1.70-1.4025 (m, 4H), 1.00-0.95 (m, 3H), 0.80-0.70 (m, 3H).

Step 4: To a solution of the amide prepared in step 3 (1.00 g, in absolute ethanol (120 mL) was 2.28 mmol) palladium(II) hydroxide (100 mg) and the reaction shaken under 55 psi of hydrogen at 60 °C overnight. The reaction was then cooled to room temperature, filtered through diatomaceous earth, and the filter cake rinsed with fresh ethanol. The concentrated under reduced pressure and filtrate was

redissolved in dry acetonitrile (15 mL). To this was added di-tert-butyl dicarbonate (650 mg, 2.96 mmol) and N, Ndiisopropylethylamine (450 uL, 2.50 mmol), and the reaction mixture stirred at room temperature overnight. The reaction then concentrated under reduced was mixture redissolved in chloroform, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless oil. Purification by flash column chromatography (silica, 66:33 10 hexanes/ethyl acetate) yielded the desired Boc-protected amine (953 mg):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 7.60-7.59 (m, 1H), 7.48-7.47 (m, 1H), 7.08-7.07 (m, 1H), 3.92 (s, 3H), 3.60-3.51 (m, 4H),3.46-3.44 (m, 2H), 3.22-3.16 (m, 6H), 1.70-1.48 (m, 13H), 1.10-0.98 (m, 3H), 0.78-0.74 (m, 3H); ESI MS m/z 448 [M + H]<sup>+</sup>. 15

Step 5: To a solution of Boc-protected amine prepared in step 4 (953 mg, 2.13 mmol) in 2:1:1 dioxane/methanol/water (14.2 mL) was added lithium hydroxide monohydrate (268 mg, 6.39 mmol), and the reaction mixture stirred at room temperature The reaction mixture was concentrated under reduced pressure and then partitioned between ethyl acetate The aqueous phase was acidified with 1 N and water. hydrochloric acid and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with 25 water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to provide 3-[4-(tert-butoxycarbonyl)piperazin-1-yl]-5the desired [(dipropylamino)carbonyl]benzoic acid (770 mg): ESI MS m/z 434 30  $[M + H]^+$ .

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Step 6: A solution of the acid from step 5 (320 mg, 0.738 mmol) and HBTU (279 mg, 0.738 mmol) in methylene chloride (4.6 mL) containing N,N-diisopropylethylamine (770  $\mu$ L, 4.42 mmol)

was stirred at room temperature for 20 minutes. To this was added a solution of (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (300 mg, 0.738 mmol) and N, Ndiisopropylethylamine (770  $\mu$ L, 4.42 mmol) in methylene chloride The reaction mixture was at room stirred (4.6 mL). reaction then The mixture was temperature overnight. concentrated under reduced pressure, diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under reduced 10 Purification by flash pressure to yield a yellow syrup. column chromatography (silica, 93:7 chloroform/methanol) gave the desired amide (443 mg): ESI MS m/z 750 [M + H]<sup>+</sup>.

Step 7: To a solution of the amide prepared in step 6 (220 mg, 15 0.293 mmol) in 1,4-dioxane (2.0 mL) was added hydrochloric acid (750  $\mu$ L, 4 M dioxane, 3.0 mmol) and the reaction mixture The reaction mixture was stirred at room temperature for 2 h. was then concentrated under reduced pressure. The residue was taken up in methylene chloride and concentrated again under 20 reduced pressure. This was repeated until a solid remained. No further purification was required. The recovered solid was dried under high vacuum over phosphorus pentoxide at 50 °C for h to give the title compound (120 mg) which was characterized as its dihydrochloride salt: mp 135-136 °C; ESI 25  $MS m/z 650 [M + H]^{+}$ .

EXAMPLE SP-297

N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxo-4-propylcyclohexyl)acetamide

Step 1: A solution of 2-propylphenol (26.83 g, 197 mmol), potassium carbonate (30.64 g, 221 mmol), methyl iodide (50.0

mL, 800 mmol), and 18-crown-6 (500 mg, 1.9 mmol) in acetone (300 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature, the solid removed by filtration, and the filtrate concentrated under reduced pressure. The resulting residue was partitioned between methylene chloride and water. The organic layer was washed with 2 N sodium hydroxide, water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to afford the desired methyl phenyl ether (23.46 g) as an oil, which was used without further purification: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.16-7.11 (m, 2H), 6.90-6.82 (m, 2H), 3.81 (s, 3H), 2.58 (m, 2H), 1.60 (tq, J = 7, 5 Hz, 2H), 0.95 (t, J = 7 Hz, 3H).

Step 2: Absolute ethanol (200 mL) followed by tetrahydrofuran 15 (50 mL) was added at -78 °C to a solution of methyl phenyl ether from step 1 (10.0 g, 66.58 mmol) suspended in anhydrous ammonia (700 mL). Lithium metal (2.3 g, 330 mmol) was added at -78 °C in small portions over 0.5 h to yield a deep blue The reaction was stirred at -78 °C until a white 20 solution resulted. The cooling bath was taken away, the flask exposed to the atmosphere, and the ammonia was removed under a stream of nitrogen. The solid residue remaining was dissolved in a minimum amount of water and acidified to pH 3 with 10% hydrochloric acid, and then extracted several times with 25 The combined ether phase was washed with diethyl ether. saturated sodium chloride, dried (sodium sulfate), filtered, and carefully concentrated under reduced pressure at 0 °C to The oil was dissolved in 10% hydrochloric provide an oil. acid (200 mL) and refluxed for 3 h. The reaction mixture was 30 then cooled to room temperature and extracted several times with diethyl ether. The combined ether extracts were washed with saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield an

oil. Purification by flash column chromatography (silica, 89:11 hexanes/ethyl acetate) gave 2-propylcyclohexenone (4.43 g):  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  6.95-6.89 (m, 1H), 5.97 (app dt, J = 10, 2 Hz, 1H), 2.39-2.36 (m, 3H), 2.20-2.04 (m, 1H), 1.88-1.63 (m, 2H), 1.50-1.25 (m, 4H), 0.93 (t, J = 7 Hz, 3H).

Step 3: A solution of sodium metal (30 mg, 1.30 mmol) in absolute ethanol (4.0 mL) was stirred at -10 °C for 0.5 h. Diethyl malonate (3.5 mL, 23 mmol) was added at -10 °C followed by addition of a solution of 2-propylcyclohexenone 10 (3.0 g, 21.7 mmol) in absolute ethanol (3.0 mL). The reaction mixture was stirred an additional 12 h at room temperature. The reaction mixture was acidified to pH 3 with hydrochloric acid and then extracted several times with diethyl ether. The combined ether extracts were washed with 15 water, and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a Purification by flash column chromatography vellow oil. (silica, 83:17 hexanes/ethyl acetate) gave 2-(3-oxo-4-propylcyclohexyl)-malonic acid diethyl ester (5.07g): <sup>1</sup>H NMR (300 20 MHz, CDCl<sub>3</sub>)  $\delta$  4.21 (q, J = 7 Hz, 2H), 4.20 (q, J = 7 Hz, 2H), 3.30 (s, 0.5H), 3.28 (s, 0.5H), 2.67-1.55 (m, 8H), 1.43-1.11(m, 10H), 0.90 (t, J = 7 Hz, 1.5H), 0.90 (t, J = 7.0 Hz, 1.5H).

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Step 4: A solution of the diester from step 2 (2.37 g, 7.94 mmol) in 1 N potassium hydroxide (16.27 mL, 16.27 mmol) was refluxed for 2 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride. The aqueous phase was acidified to pH 1-2 with 6 N hydrochloric acid and then refluxed for 2 h. The reaction mixture was cooled to room temperature and extracted several times with methylene chloride. The combined organic phase was washed with water, and saturated sodium chloride, dried

(sodium sulfate), filtered, and concentrated under reduced pressure to yield a light yellow oil. Purification by flash column chromatography (silica, 66:33 hexanes/ethyl acetate with 1% glacial acetic acid) gave (3-oxo-4-propyl-cyclohexyl)-acetic acid (1.42 g): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.71-1.12 (m, 14H), 1.11-0.82 (m, 3H); ESI MS m/z 197 [M - H]<sup>-</sup>.

Step 5: To a stirred solution of the acid from step 4 (244 mg, 1.23 mmol) and N, N-diisopropyl ethylamine (214  $\mu L$ , 1.23 mmol) in methylene chloride (7.0 mL) was added HBTU (513 mg, 1.35 10 mmol) and the reaction mixture stirred for 0.5 h. above solution was added a solution of amine (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2-ol (500 mg, 1.35 mmol) and N, N-diisopropylethylamine (428  $\mu$ L, 2.46 mmol) in methylene chloride (7.0 mL) and the reaction mixture 15 was stirred under nitrogen for 18 h. The reaction mixture was then diluted with additional methylene chloride and washed with saturated sodium bicarbonate, 0.5 N hydrochloric acid, and saturated sodium chloride. The organic layer was then dried (sodium sulfate), filtered, and concentrated under 20 reduced pressure to yield an oily residue. Purification by flash column chromatography (silica, 7:93 methanol/methylene chloride) gave the title compound (360 mg): mp 52-54 °C; ESI MS m/z 515 [M + H]<sup>+</sup>.

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EXAMPLE SP-298

 $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-2-(3-oxocyclohexyl)acetamide$ 

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Step 1 (3-0xo-cyclohexyl)-malonic acid diethyl ester was prepared in 88% yield from cyclohexenone by the method described above for the synthesis of 2-(3-oxo-4-propyl-

cyclohexyl)-malonic acid diethyl ester:  $^{1}$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.44-4.12 (m, 4H), 2.88-1.22 (m, 16H).

Step 2 (3-Oxo-cyclohexyl)-acetic acid was prepared in 70% yield from 2-(3-oxo-cyclohexyl)-malonic acid diethyl ester by the method described above for the synthesis of (3-oxo-4-propyl-cyclohexyl)-acetic acid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.58-1.92 (m, 7H), 1.80-1.61 (m, 1H), 1.52-1.42 (m, 1H); ESI MS m/z 155 [M - H].

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Step 3: N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxocyclohexyl)acetamide was prepared in 23% yield from (3-0xo-cyclohexyl)-acetic acid by the method described for the synthesis of N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxo-4-propylcyclohexyl)acetamide (EXAMPLE SP-297.)

mp 139.5-149.8 °C;); ESI MS m/z 473 [M + H]<sup>+</sup>.

### 20 EXAMPLE SP-299

3-benzyl-4-(4-butylphenyl)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxobutanamide

Step 1: Benzaldehyde (2.81 mL, 27.15 mL) was added at 0  $^{\circ}\text{C}$  to 25 a solution of 4-butyl-acetophenone (5.26 mL, 27.15 mmol) in methanol (7.8 mL) and water (13.0 mL) containing sodium hydroxide (1.39 g, 34.75 mmol). The reaction was warmed to The reaction mixture was room temperature and stirred 48 h. diluted with ethyl acetate and washed with water, saturated 30 sulfate), dried (sodium filtered, chloride, sodium concentrated to yield a light yellow syrup. impurities were removed under high vacuum at 120 °C to yield the desired enone (6.3 g): ESI MS m/z 265 [M + H]<sup>+</sup>.

Step 2: A solution of the enone prepared in step 1 (2.0 g, 7.56 mmol) in anhydrous diethyl ether (11 mL) was added at -78 °C to a solution of lithium metal (120 mg, 16.6 mmol) in dry liquid ammonia (11 mL). The reaction was stirred at -78 °C for 0.5 h and excess lithium was quenched with several drops piperylene to yield a yellow solution. bromoacetate (2.75 g, 18.9 mmol) was added in one portion and the reaction stirred at -78 °C for 0.5 h then at -33 °C for 2 The reaction was then quenched with NH4Cl and the open 10 reaction vessel warmed to room temperature. The residue was partitioned between ethyl acetate and water and the phases separated. The organic phase was washed with water, saturated (sodium sulfate), filtered chloride, dried sodium concentrated to yield a yellow syrup. Purification by flash 15 hexanes/ethyl 74:25:1 chromatography (silica, column gave 3-benzyl-4-(4-butylphenyl)-4acetate/acetic acid) oxobutanoic acid (60 mg): ESI MS m/z 325 [M + H]<sup>+</sup>.

Step 3: A solution of 3-benzyl-4-(4-butylphenyl)-4-oxobutanoic 20 acid (60 mg, 0.185 mmol) and HBTU (70 mg, 0.185 mmol) in mL) containing (1.2)chloride methylene diisopropylethylamine (100  $\mu\text{L}$ , 0.55 mmol) was stirred at room temperature for 20 minutes. To this was added a solution of (2R, 3S) - 3 - amino - 4 - (3, 5 - diffluorophenyl) - 1 - [(3 - amino - 4 - (3, 5 - diffluorophenyl)]25 amine ethylbenzyl)amino]butan-2-ol (75 mg, 0.185 mmol) and N, Ndiisopropylethylamine (100  $\mu$ L, 0.55 mmol) in methylene chloride The reaction mixture was stirred at room (1.2)mL). The reaction mixture was then temperature overnight. concentrated under reduced pressure, diluted with methylene 30 chloride, washed with saturated sodium bicarbonate, water and saturated sodium chloride, dried (sodium sulfate), filtered, and concentrated under reduced pressure to yield a colorless Purification by flash column chromatography (silica,

93:7 chloroform/methanol) gave the title compound (36 mg) (diastereomeric mixture): mp 42-45 °C; ESI MS m/z 641 [M + H]<sup>+</sup>.

EXAMPLE SP-300

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 $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-indol-6-ylmethyl)amino]propyl\}-5-methyl-N^3,N^3-dipropylisophthalamide$ 

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Step 1: To a -78 °C, stirred solution of methyl 1H-indole-6-carboxylate (500 mg, 2.85 mmol) in methylene chloride (11.5 mL) was added diisobutylaluminum hydride (5.70 mL, 1.0 M solution in methylene chloride). The reaction mixture was stirred for 2 h at -78 °C, and slowly warmed to room temperature for 10 h. The reaction mixture was quenched with methanol, washed with Rochelle's salt (saturated aqueous

potassium sodium tartrate), dried (magnesium sulfate), and concentrated under reduced pressure. Purification by flash column chromatography (silica, 6:1 ethyl acetate/hexanes) afforded an alcohol (100 mg):  $^1$ H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.21 (br s, 1H), 7.62 (d, J = 9 Hz, 1H), 7.39 (s, 1H), 7.20-7.22 (m, 1H), 7.10-7.13 (m, 1H), 6.54-6.56 (m, 1H), 4.77 (d, J = 3 Hz, 2H), 1.60 (s, 1H).

Step 2: To a stirred solution of alcohol from step 1 (100 mg, 0.68 mmol) in methylene chloride (3 mL) was added magnesium 10 oxide (590 mg, 6.8 mmol) and the reaction mixture was stirred reaction mixture was filtered through The diatomaceous earth and concentrated under reduced pressure to provide 1H-indole-6-carbaldehyde (99 mg) as a solid, which was 15 carried forward without further purification characterization. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 10.03-10.88 (m, 1H), 8.56 (br s, 1H), 7.96 (s, 1H), 7.74 (d, J = 8 Hz, 1H), 7.64-7.70 (m, 1H), 7.46 (t, J = 3 Hz, 1H), 6.65 (s, 1H).

Step 3: To a stirred solution of 1H-indole-6-carbaldehyde (99 20 and tert-butyl (1S, 2R) - 3 - amino - 1 - (3, 5 - 3)mmol) difluorobenzy1)-2-hydroxypropylcarbamate acetate 3 (256 mg, 0.68 mmol) in 2-propanol (3 mL) was added sodium borohydride (30 mg, 0.82 mmol). The reaction mixture was stirred for 12 25 h., quenched with methanol, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 ethyl acetate/hexanes) provided indole (50 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ 8.41 (br s, 1H), 7.60 (d, J = 8 Hz, 1H), 7.38 (s, 1H), 7.21 (t, J = 3 Hz, 1H), 7.04 (dd, J = 8, 1 30 Hz, 1H), 6.71-6.73 (m, 3H), 6.61-6.68 (m, 1H), 6.53 (s, 1H), 5.38 (br s, 2H), 4.66 (d, J = 9 Hz, 1H), 3.89 (s, 2H), 3.49-3.54 (m, 1H), 2.91-2.98 (m, 1H), 2.62-2.73 (m, 3H), 1.35 (s, 9H).

Step 4: To a stirred solution of indole from step 3 (50 mg, 0.11 mmol) was added hydrochloric acid (0.27 mL, 4.0 M solution in dioxane). The reaction mixture was stirred for 1 h, diluted with ethyl ether, and concentrated under reduced pressure to provide (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1H-indol-6-ylmethyl)amino]butan-2-ol hydrochloride 4 (70 mg): ESI MS <math>m/z 346  $[M + H]^+$ .

Step 5: To a stirred solution of 3-[(dipropylamino)carbonyl]-10 5-methylbenzoic acid (5) (29 mg, 0.11 mmol) in methylene chloride (3 mL) was added HBTU (64 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol), and N,N-diisopropylethylamine (0.075 mL, 0.44 mmol), followed by (2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-[(1H-indol-6-ylmethyl)amino]butan-2-ol hydrochloride 4 (70 15 mg, 0.11 mmol). The reaction mixture was stirred for 12 h, diluted with methylene chloride, washed with water, saturated sodium bicarbonate, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 89:10:1 chloroform/methanol/ammonium hydroxide) provided 20 the title compound (6) (13 mg): mp 135-137 °C; ESI MS m/z 591 [M + H]<sup>+</sup>.

## EXAMPLE SP-301

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N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-25 hydroxypropyl}-1,3-benzodioxole-5-carboxamide

To a solution of piperonylic acid (0.500g, 3.01 mmol), EDC (0.867g, 4.52 mmol), HOBT (0.611g, 4.52 mmol) in anhydrous DMF (10 mL) was added a solution of TEA (1.67 mL, 12.04 mmol), 3-Amino-4-(3,5-difluoro-phenyl)-1-(3-ethyl-benzylamino)-butan-

2-ol (1.693g, 3.01 mmol), and anhydrous DMF (5 mL). Reaction mixture was stirred under nitrogen overnight. Quenched reaction mixture with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate. Washed organic layer with 1N HCl, followed by a wash with 10% sodium bicarbonate (aq.). Dried organic layer over magnesium sulfate, filtered, then concentrated in vacuo, yielding the product. (ES+: 483.2)

#### EXAMPLE SP-302

10 tert-butyl (1S,2R)-1-[3-(benzyloxy)-5-fluorobenzyl]-3-[(3-ethylbenzyl)amino]-2-hydroxypropylcarbamate

[2-(3-Benzyloxy-5-fluoro-phenyl)-1-oxiranyl-ethyl]-

carbamic acid tert-butyl ester (3.33 g, 8.59 mmol) and m-ethyl benzylamine (2.32 g, 17.19 mmol) were dissolved in isopropyl alcohol (80 ml) and brought to reflux for 2h. Reaction mixture was then concentrated in vacuo to remove isopropyl alcohol. Dissolved yellow liquid in ethyl acetate (30 ml), then washed with 1N HCl (3x100 ml). Aqueous layers were combined then extracted with ethyl acetate (2x100 ml). Organic layers were washed with 10% sodium bicarbonate (aq., 3x100 ml), followed by a brine wash. Organic layer was dried over sodium sulfate, filtered, then concentrated in vacuo, yielding the product (4.31 g). (ES+: 523.9)

EXAMPLE SP-303

5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-5-

30 oxopentanoic acid

To a solution of 3-Amino-4-(3,5-difluoro-phenyl)-1-[1-(3-mino-4-(3-minoethyl-phenyl)-cyclopropylamino]-butan-2-o1 5 (0.500q,1.387 mmol) in chloroform (7 ml) was added TEA (0.58 ml, 4.161 mmol) with stirring under nitrogen for 30 min. To this solution was added glutaric anhydride (0.158g, 1.387 mmol) and reaction was stirred overnight 50°C. at The reaction mixture was concentrated in vacuo, yielding the product. (ES+: 475.2) 10

EXAMPLE SP-304

4-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-4-oxobutanoic acid

To a solution of 3-Amino-4-(3,5-difluoro-phenyl)-1-[1-(3-ethyl-phenyl)-cyclopropylamino]-butan-2-ol (0.500g, 1.387 mmol) in chloroform (7 ml) was added TEA (0.58 ml, 4.161 mmol) with stirring under nitrogen for 30 min. To this solution was added succinic anhydride (0.138g, 1.387 mmol) and reaction was stirred overnight at 50°C. The next morning reaction mixture was concentrated in vacuo, yielding the product. (ES+: 461.2)

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EXAMPLE SP-305

formic acid compound with  $N^1-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N^5-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)pentanediamide 5 (1:1)$ 

To a solution of R-aminoquinuclidine (0.084g, 0.421 mmol)

TEA (0.294 ml, 2.11 mmol), and anhydrous DMF (2.5 ml) was

10 added 5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-5
oxopentanoic acid (0.200g, 0.421 mmol), EDC (0.121g, 0.632 mmol), HOBT (0.085g, 0.632 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10%

15 sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.122g). Prep-HPLC yielded the product as its formate salt. (ES+: 583.3)

EXAMPLE SP-306

formic acid compound with  $N^1-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N^5-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)pentanediamide (1:1)$ 

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To a solution of S-aminoquinuclidine (0.084g, 0.421 mmol) TEA (0.294 ml, 2.11 mmol), and anhydrous DMF (2.5 ml) was added 5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-5- oxopentanoic acid (0.200g, 0.421 mmol), EDC (0.121g, 0.632 mmol), HOBT (0.085g, 0.632 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.065g). Prep-

HPLC yielded the product as its formate salt. (ES+: 583.3)

#### EXAMPLE SP-307

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formic acid compound with  $N^1-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-N^4-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-yl]-N^4-(3-yl]-3-{[1-(3-yl]-3-yl]-3-[1-(3-yl]-3-yl]-3-{[1-(3-yl]-3-yl]-3-[1-(3-yl]-3-[1-(3-yl]-3-yl]-3-[1-(3-yl]-3-[$ 

ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)succinamide (1:1)

To a solution of R-aminoquinuclidine (0.086g, 0.434 mmol)

TEA (0.302 ml, 2.17 mmol), and anhydrous DMF (2.5 ml) was added 4-[((1s,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-4-oxobutanoic acid (0.200g, 0.434 mmol), EDC (0.125g, 0.651 mmol), and HOBT (0.088g, 0.651 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.200g). Prep-HPLC yielded the product as its formate salt. (ES+: 569.3)

EXAMPLE SP-308

formic acid compound with N¹-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-N⁴-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)succinamide

5 (1:1)

To a solution of S-aminoquinuclidine (0.086g, 0.434 mmol)

TEA (0.302 ml, 2.17 mmol), and anhydrous DMF (2.5 ml) was added 4-[((1s,2r)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-4-oxobutanoic acid (0.200g, 0.434 mmol), EDC (0.125g, 0.651 mmol), and HOBT (0.088g, 0.651 mmol) under nitrogen, with stirring at 45°C overnight. Reaction mixture was quenched with 10% sodium bicarbonate (aq.) then extracted with ethyl acetate then concentrated in vacuo, yielding product (0.093g). Prep-HPLC yielded the product as its formate salt. (ES+: 569.3)

EXAMPLE SP-309

MP stands for macroporous resin.

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2: A solution of 1 (2.50g; 5.75mmol) and DIEA (1.20mL; 6.90mmol) in DCM (100mL) was cooled in an ice/water bath. Allyl chloroformate (0.73mL; 6.90mmol) was added, and the reaction was allowed to come to ambient temperature over 4h. The reaction was washed with 10% K<sub>2</sub>CO<sub>3</sub> (100mL), water (100mL), brine (100mL), and dried over Na<sub>2</sub>CO<sub>3</sub>. Flash chromatography on 90g silica gel with 0-30% EtOAc/ heptane afforded 2.88g (5.55mmol; 96%) 2 as a white solid.

3: A solution of 2 (2.88g; 5.55mmol) and Dowex 50WX2 (Aldrich; 8.88g; approx. 44.4mmol) in MeOH (100mL) was heated to 50°C for 5.25h. The reaction was cooled to ambient temperature and filtered. The resin was washed well with MeOH, and the product was eluted with approx. 3.5M ammonia in MeOH. After removal of solvent, 2.11g (5.04mmol; 91%) 3 was collected as an off-white waxy solid.

- 5: The appropriate amines (0.3mmol) were added to vials containing 4-(chlorosulfonyl)benzoic acid 4 (2.0mL of a 0.05M solution of THF) plus 1eq. of DIEA if necessary (to liberate any amine hydrochloride salts). The vials were agitated on an orbital shaker at ambient temperature/250rpm for 18h. Mp-isocyanate resin (approx. 0.6mmol) was added to each vial, which were heated to 60°C for 5h. The reactions were filtered, the resin washed well with THF, and concentrated.
- 6: The acids 5 were coupled to Alloc-protected TSI 3 using 20 HATU (1.2eq.) and DIEA (2.4eq.) in DMF for 18h at ambient temperature. MP-isocyanate (3eq.) and MP-carbonate (1eq.) were then added, and the reactions rocked for 4h at ambient temperature. The reactions were filtered, the resins washed well with 1,2-dichloroethane, and concentrated. The residues 25 were dissolved in 1,2-dichloroethane (1.5mL), washed with 1M citric acid (1.5mL) and loaded onto 3mL capacity Varian ChemElut Hydromatrix cartridges. After 5 min, the product was eluted with 1,2-dichloroethane (2x6mL), and concentrated in vacuo.

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7: Alloc intermediates 6 were deprotected using Pd(Ph3P)4 (0.15eq.) and 1,3-dimethylbarbituric acid (20eq.) in THF at 60°C/3h. The reaction vials were concentrated in vacuo, and SCX was performed by loading the crude reaction mixture onto

1000mg/3mL SCX cartridges using 5mL MeOH. The cartridges were washed well with MeOH, and the products eluted with approx.

3.5M ammonia in MeOH. If necessary, the final products were purified by high-throughput preparative UV HPLC.

The following compounds were prepared using the above described methodology.

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EXAMPLE	Structure	Compound Name(s)	OAMS
2065	H N OH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-phenylpropanamide	467.3
2965	N OH N OH N HCOOH	formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[ethyl(methyl)amino] sulfonyl}benzamide	560.1
2966	ONS CHARLES	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(piperidin-1-ylsulfonyl)benzamide	586.2
2968	H N OH F	2-(2-chlorophenoxy)- N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}acetami de	503.3

			441 0
	N H	N-{(1S,2R)-1-(3,5-	441.2
	N A A F	difluorobenzyl)-3-	
		[ (3-	
1	الرام الم	ethylbenzyl)amino]-2-	
	OH Y	hydroxypropyl}pyrazin	. 1
	∠NH F	e-2-carboxamide	
1			
0050	~ ]		
2969		N-{(1S,2R)-1-(3,5-	531.2
	O H	difluorobenzyl)-3-	334.2
		•	
	OH OH	[(3-	ŀ
	NH F	ethylbenzyl)amino]-2-	1
	(""'	hydroxypropyl}-3-	
		(phenylsulfonyl)propa	
		namide	[ ]
2970	~ ]		<u> </u>
	Q, p	formic acid compound	589.9
	NE DH L	with N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	[ ]
}	Ů <sup>™</sup> √F	3-[(3-	}
	нсоон	ethylbenzyl)amino]-2-	
	F ACCOR	hydroxypropyl}-4-	
	·	(1,3-thiazolidin-3-	
		ylsulfonyl)benzamide	
2971		(1:1)	634 0
		formic acid compound	1 1
		with N-{(1S,2R)-1-	1 1
	F	(3,5-difluorobenzyl)-	
		3-[(3-	
	F HCOOH	ethylbenzyl)amino]-2-	1
		hydroxypropyl}-4-	
		(3,4-	
1		dihydroisoquinolin-	
1		2(1H)-	
		ylsulfonyl)benzamide	
2972		(1:1)	
2312	0,8	N-{(1s,2r)-1-(3,5-	663.0
1	N DH H OH H	difluorobenzyl)-3-	,
		[(3-	
1	0 YF	ethylbenzyl)amino]-2-	.
1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	hydroxypropyl}-4-[(4-	
•		phenylpiperazin-1-	
2973	0.0	yl)sulfonyl]benzamide	
		formic acid compound	
		with N-{(1s,2R)-1-	
	<sub>F</sub>   0 \ \ \ \ \ \ \	(3,5-difluorobenzyl)	-
	[ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	3-[(3-	
2974	F HCOOH	ethylbenzyl)amino]-2-	-
47/4	НСООН	13 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	

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1		fluorophenyl)piperazi	
		n-1-	
		yl]sulfonyl}benzamide	
		(2:1)	
	0, 0	N-{(1S,2R)-1-(3,5-	572
	~NS OH	difluorobenzyl)-3-	
		[(3-	
	0	ethylbenzyl)amino]-2-	
ļ.		hydroxypropyl}-4-	
	Ė	(pyrrolidin-1-	
2975		ylsulfonyl)benzamide	
4915	0.0	formic acid compound	572 0
		with $N-\{(1S,2R)-1-$	3,2.0
		(3,5-difluorobenzyl)-	
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	TT.	3-[(3-	
	НСООН	ethylbenzyl)amino]-2-	
	F	hydroxypropyl}-4-	
		(pyrrolidin-1-	
		ylsulfonyl)benzamide	
2976		(1:1)	
	<b>%</b>	formic acid compound	731.0
		with $N-\{(1S, 2R)-1-$	
		(3,5-difluorobenzyl)-	
	СБ, НСООН	3-[(3-	
	- нсоон	ethylbenzyl)amino]-2-	
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2977		(2:1)	546
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		[(3-	
	0 \\F	ethylbenzyl)amino]-2-	
		hydroxypropyl}-4-	
	ļ Ė	[(dimethylamino)sulfo	
2978		nyl]benzamide	
•	0,0	formic acid compound	
	N'S U OH L	with $N-\{(1S,2R)-1-$	
		(3,5-difluorobenzyl)-	
	0 <b>F</b>	3-[(3-	
	нсоон		
	Į ,	hydroxypropyl}-4-	
		[(dimethylamino)sulfo	
2979		nyl]benzamide (1:1)	Į.
4313	l	INATINETISMITUE (T:T)	<del></del>

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		difluorobenzyl)-3-	ļ
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		hydroxypropyl}benzami	
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		]sulfonyl}-N-	
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	F	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2981		de (1:1)	
2501	0, 0	formic acid compound	588.1
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	т нсоон F	ethylbenzyl)amino]-2-	
j		hydroxypropyl}-4-	
		(morpholin-4-	,
		ylsulfonyl)benzamide	
2982		(1:1)	
	9,9	formic acid compound	585.0
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	[	difluorobenzyl)-3-	
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		1 * *	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2983		de (1:1)	644
	💖	formic acid compound	614.0
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		{[cyclohexyl(methyl)a	
	♥ F	mino]sulfonyl}-N-	
	нсоон	{(1\$,2R)-1-(3,5-	
	ļ <u></u>	difluorobenzyl)-3-	
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		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2004		<del>-</del>	
2984		de (1:1)	L

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		formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-	
	N HCOOH	3-[(3-  ethylbenzyl)amino]-2-	
	F нсоон	hydroxypropyl}-4-	
		{[methyl(2-pyridin-2-	
2985		ylethyl) amino] sulfony 1} benzamide (2:1)	
2303	0,0	formic acid compound	608.1
,	N'S H OH H	with N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	нсоон	3-[(3-  ethylbenzyl)amino]-2-	
	ļ ļ	hydroxypropyl}-4-	
		{[methyl(phenyl)amino	
2986		sulfonyl benzamide  (1:1)	
	No.	formic acid compound	622.1
	NO N	with 4-	
		{ [benzyl (methyl) amino ] sulfonyl } -N-	
	Нсоон	{(1S, 2R) -1-(3, 5-	
	ŗ	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}benzami	
2987		de (1:1)	
		formic acid compound	636.1
		with $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-$	
		3-[(3-	
	нсоон	ethylbenzyl)amino]-2-	
	'	hydroxypropyl}-4- {[methyl(2-	
		phenylethyl)amino]sul	
2988	0.0	fonyl}benzamide (1:1)	
		formic acid compound with 4-	572.1
		{[allyl(methyl)amino]	
		sulfonyl}-N-{(1S,2R)-	İ
	НСООН	1-(3,5-	
	· ·	difluorobenzyl)-3- [(3-	•
		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2989		de (1:1)	

		formic acid compound with 4-{[[2-(diethylamino)ethyl](	631.1
	нсоон	methyl)amino]sulfonyl	
	Е нсоон	}-N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3- [(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2990		de (2:1)	
		formic acid compound	574.1
	N OH H OH	with N-{(1S,2R)-1-	
	F	(3,5-difluorobenzyl)- 3-[(3-	
		ethylbenzyl)amino]-2-	
	нсоон	hydroxypropyl}-4-	
		{[methyl(propyl)amino	
2001		sulfonyl}benzamide	
2991	0 0	(1:1)	E00 1
	N 0H	formic acid compound with 4-	288.1
		{[butyl(methyl)amino]	
	,	$sulfonyl}-N-{(1S,2R)-}$	
	НСООН	1-(3,5-	
	<b>F</b>	difluorobenzyl)-3-	
		[(3-  ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2992		de (1:1)	
	9,0	formic acid compound	602.1
	N'S H ÔH H	with N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	нсоон	3-[(3- ethylbenzyl)amino]-2-	
	F	hydroxypropyl}-4-	
		{[methyl(pentyl)amino	.
		]sulfonyl}benzamide	
2993		(1:1)	
		formic acid compound	602.1
		with N-{(1S,2R)-1-	
	F	(3,5-difluorobenzyl)- 3-[(3-	
	нсоон	ethylbenzyl)amino]-2-	
	Ė	hydroxypropyl}-4-	
		{[isopentyl(methyl)am	
2004		ino]sulfonyl}benzamid	
2994		e (1:1)	

			615 0
	0,0	formic acid compound	615.0
	N,g H OH H	with $N-\{(1S, 2R)-1- $	
		(3,5-difluorobenzyl)-	I
	)₁_/ Ö - F	3-[(3-	
	́ нсоон	ethylbenzyl)amino]-2-	ł
	Ė нсоон	hydroxypropy1}-4-	
	·	{[methyl(1-	
İ		methylpyrrolidin-3-	
	e.	yl)amino]sulfonyl}ben	
2995	•	zamide (2:1)	
2775	0, 0	formic acid compound	602.0
	VNS U OH U	with $N-\{(1S, 2R)-1-$	
		(3,5-difluorobenzyl)-	
	Ö 🍆 F	3-[(3-	
	<b>∀</b> нсоон	ethylbenzyl)amino]-2-	
	Ė	hydroxypropyl}-4-	'
		[(dipropylamino)sulfo	
2006		nyl]benzamide (1:1)	
2996	0. 0	formic acid compound	574.0
		with 4-	
		[(diethylamino)sulfon	
	F		
		y1]-N-{(1S,2R)-1-	
	нсоон	(3,5-difluorobenzyl)-	
	·	3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}benzami	
2997		de (1:1)	<u>l</u>

# EXAMPLE SP-310

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 $N-\{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl\}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide$ 

ethyl 2-amino-1,3-oxazole-4-carboxylate

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To a 250 ml 3-neck round bottom flask was added (20g, 0.3332 moles) urea, (150ml) ethanol and (42.42g, 0.2175 The mixture was then moles, 0.65eq) ethylbromopyruvate. heated under agitation to reflux for 16 hours. The reaction solution changed from yellow to red in color. The reaction solution was then evaporated to dryness and the crude product was taken up in (50ml) water and (150ml) ethyl acetate. pH was adjusted from 1 to 10 using 2N sodium hydroxide, changing the biphasic mixture a dark red. The mixture was separated and the aqueous phase was extracted twice with ethyl acetate. The organic layers were then combined and washed with water and brine. The resulting yellow solution was concentrated to ~50ml, causing an off-white solid to precipitate out. The solid was filtered off and washed with ethanol and diethyl ether. The mother liquor was then evaporated to dryness and the resulting oily solid was taken up in (150ml) ethyl acetate and concentrated to ~50ml. off-white solid precipitated out. The mixture was cooled in an ice bath, and the solid was filtered off and washed with

ethanol and diethyl ether to give ethyl 2-amino-1,3-oxazole-4-carboxylate (14.79 g).

ethyl 2-[(methylsulfonyl)amino]-1,3-oxazole-4-carboxylate To a 20 ml screw cap vial was added (1g, 5.8069 Step 2. 5 ethyl 2-amino-1,3-oxazole-4-carboxylate, dichloromethane and (1.39ml, 7.9797mmoles, 1.25 eq.) N,N-To the reaction was then added diisopropylethylamine. (0.545ml, 7.0415 mmoles, 1.1 eq.) methanesulfonyl chloride, and the reaction was agitated for 14 hours. The reaction was 10 then evaporated to dryness and purified using a Biotage silica (272mg) of ethyl 2resulting in gel column, [(methylsulfonyl)amino]-1,3-oxazole-4-carboxylate.

2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4carboxylate

Step 3. To a 25 ml round bottom flask under  $N_2$  was added (101.8mg, 0.4346 mmoles) ethyl 2-[(methylsulfonyl)amino]-1,3oxazole-4-carboxylate, (180.2mg, 1.3038 mmoles, potassium carbonate, and (5ml) acetonitrile. The mixture was 20 then agitated at ambient temperature while  $(33.8\mu l, 0.5429)$ mmoles, 1.25 eq.) iodomethane was added. The reaction was allowed to run at ambient temperature for 3 hours. electrospray mass spec indicated mostly starting material. The  $N_2$  line was removed and an additional (40 $\mu$ l, 0.6425 mmoles, 25 1.5 eq.) iodomethane were added. The reaction was left at ambient temperature overnight. The reaction was quenched with (5ml) 1N HCl and was extracted with dichloromethane. The organic layer was washed with water and then evaporated to dryness. The resulting oil was purified by preparative HPLC, 30 yielding (70mg) of ethyl 2-[methyl(methylsulfonyl)amino]-1,3oxazole-4-carboxylate.

2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylic acid To a 50 ml round bottom flask was added (61mg, 2-[methyl(methylsulfonyl)amino]-1,3-0.2457 mmoles) ethyl oxazole-4-carboxylate, (51.5mg, 5.0 1.2274 mmoles, lithium hydroxide, (2.5ml) tetrahydrofuran and (1.5ml) water. The reaction was agitated at ambient temperature for ~2 hours. The reaction was complete by electrospray mass spec. reaction was worked up by adding (5ml) 1N HCl and then extracting with ethyl acetate. The organic layer was washed with water and brine and then dried with magnesium sulfate. 10 The solution was then evaporated to dryness, leaving (44.6mg) 2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxylic acid.

N-{(1s, 2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide

14.7

To a 7 ml screw cap vial was added (20.9mg, Step 5. 0.0949 mmoles) 2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4carboxylic acid, (36.7mg, 0.1097 mmoles, 1.15 eq.) (2R,3S)-3-20 amino-4-(3,5-difluorophenyl)-1-[(3-ethylbenzyl)amino]butan-2ol and (54.6mg, 0.1436 mmoles, 1.5 eq.) HATU, followed by (1.25ml) N,N-dimethylformamide. The reaction was placed in an orbital shaker and was left at ambient temperature for 2 The reaction was quenched with (2ml) 1N HCl. 25 hours. clear solution was extracted three times with ethyl acetate and the combined organic layers were washed with saturated sodium carbonate solution and then brine. The solution was then dried with magnesium sulfate and evaporated to a clear oil which was purified by preparative HPLC, resulting N-30  $\{(1S, 2R)-1-(3, 5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-\}$ hydroxypropyl}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4carboxamide (15.7mg).

EXAMPLE SP-311

methyl 3-cyano-5-[(dipropylamino)carbonyl]benzoate

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Methyl 3-bromo-5-[(dipropylamino)carbonyl]benzoate (Preparation 3) (0.15 g), copper (I) cyanide, and N-methylpyrrolidinone (1 mL) was heated at 150 °C overnight, at which time the mixture was cooled and partitioned between ethyl acetate and aq. HCl (1N). The organic layer was dried (magnesium sulfate), concentrated under reduced pressure, and the residue was chromatographed on silica gel using ethyl acetate-hexane (20/80) to give 0.066 g of the desired product. ms (m + H) 289.2. See also preparation 7 for the preparation of the acid.

EXAMPLE SP-312

(2R,3S)-3-amino-4-(3,5-difluorophenyl)-1-{[3-(trifluoromethyl)benzyl]amino}butan-2-ol dihydrochloride

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$$F \xrightarrow{\qquad \qquad \qquad } F \xrightarrow{\qquad } F \xrightarrow{\qquad \qquad } F \xrightarrow{\qquad $

A mixture of oxirane (1.0 g) and 3-25 (trifluoromethyl)benzylamine (1.2 g) in isopropyl alcohol (25 mL) was stirred at reflux for 4 h, at which time the mixture was cooled and the solvent was removed under reduced pressure.

The residue was partitioned between ethyl acetate and aq. HCl (1N) and the organic layers were dried (sodium sulfate), concentrated, and chromatographed on silica gel using methanol-dichloromethane (5/95) to give 1.0 g of tert-butyl (1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[3-(trifluoromethyl)benzyl]amino}propylcarbamate.

The carbamate group was then removed essentially using the method described in EXAMPLE SP-272.

## 10 EXAMPLE SP-313

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3-[(dipropylamino)carbonyl]-5-ethynylbenzoic acid

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Step 1: A solution of methyl 3-bromo-5- [(dipropylamino)carbonyl]benzoate (25) (200 mg, 0.58 mmol), PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (16 mg, 0.03 mol %) and CuI (6 mg, 0.05 mol %) in triethylamine (1.2 mL) was heated to reflux. (Trimethylsilyl) acetylene (100  $\mu$ L, 0.7 mmol) was added, and the bright yellow solution quickly turned orange then went brown within a minute. The reaction mixture was stirred for 3 h, cooled to room temperature, diluted with H<sub>2</sub>O (20 mL), and extracted with CHCl<sub>3</sub> (3 x 15 mL). The combined organics were washed with

saturated NaCl (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to give methyl 3- [(dipropylamino)carbonyl]-5-[(trimethylsilyl)ethynyl]benzoate 26 (185.5 mg):  $^1$ H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.95 (s, 1H), 7.75 (s, 1H), 7.43 (s, 1H), 3.74 (s, 3H), 3.25 (br s, 2H), 2.95 (br s, 2H), 1.49 (br s, 2H), 1.34 (br s, 2H), 0.79 (br s, 3H), 0.56 (br s, 3H), 0.06 (s, 9H).

methyl of solution 2: То а stirred Step [(dipropylamino)carbonyl]-5-[(trimethylsilyl)ethynyl]benzoate 10 26 (185.3 mg, 0.49 mmol) in MeOH (2.5 mL) was added a solution of KOH (2.9 mL of a 1 M solution in H<sub>2</sub>O, 2.9 mmol). resulting homogeneous brown solution turned to a white/brown suspension, then to a clear brown solution. The reaction mixture was stirred for 4 h, diluted with CHCl<sub>3</sub> (40 mL), 15 separated and the organic layer was concentrated under reduced provide 3-[(dipropylamino)carbonyl]-5pressure to ethynylbenzoic acid 27 (141.8 mg):  $^1\text{H}$  NMR (300 MHz, CDCl3):  $\delta$ 8.22 (d, J = 1 Hz, 1H), 8.05 (d, J = 1 Hz, 1H), 7.71 (d, J = 1Hz, 1H), 3.48 (br.s, 2H), 3.17 (s, 1H), 3.16 (br.s, 2H), 1.71 20 (d, J = 7 Hz, 2H), 1.55 (d, J = 7 Hz, 2H), 1.00 (d, J = 7 Hz,3H), 0.78 (d, J = 7 Hz, 3H).

The following compounds were also prepared using the procedures described above and the schemes described below.

		Compound Name(s)	Mass
EXAMPLE	Structure	Compound Name(s)	Spec
	HO NO HONDON HON	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-hydroxyethyl)(methylsulfonyl)amino]benzamide	*575.3
2999	Dr.	5-bromo-N <sup>1</sup> -{(1S,2R)-1-	
3000	H OH H	(2,4-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N³,N³- dipropylisophthalamide	**644 646
	O H OH H HCI	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(2-methoxyethyl)(methylsulfonyl)amino]benzamidehydrochloride	**590
3001	O H OH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(methylsulfonyl)methylbenzamide	**531
3003	OSSO OH  N OH H  N OH  N OH H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(4-hydroxybutyl)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamidehydrochloride	**702
3004	H QH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(dipropylamino)isoquinoline-7-carboxamide	**589.4

3005	P O H H D H H D H H D H H D H H D H H D H H D H H D H H D H H D H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-{[(2-hydroxyethyl)(methyl)amino]sulfonyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	**703
3006	H OH H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(ethylamino)sulfonyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	**673
3007		N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-(5- methyl-1,2,4- oxadiazol-3-yl)-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide hydrochloride	**648.4
3008	O-S-O O F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[methyl(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	**** 537.3 (+)
3009	N N H OH H	N <sup>1</sup> -{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylmalonamide	
3010	F F O N H O H O O O O O O O O O O O O O O O	N <sup>2</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> - dipropylbicyclo[2.2.1] hept-5-ene-2,3- dicarboxamide	

N <sup>1</sup> -{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-	
F ethylbenzyl)amino]-2-	
hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -	
dipropylcyclopentane-	1
N	1
3011	
$N^2 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
f difluorobenzyl)-3-[(3-	İ
ethylbenzyl)amino]-2-	
hydroxypropyl}-3,4-	
dimethyl-N <sup>5</sup> , N <sup>5</sup> -	
dipropylthieno[2,3-	
b]thiophene-2,5-	
3012 dicarboxamide	
difluorobenzy1) -3-[(3-	
ethylbenzyl) amino] -2-	
hydroxypropy1}-2-	]
phenyl-N <sup>5</sup> , N <sup>5</sup> -	l
dipropylpentanediamide	
3013	
N <sup>2</sup> -benzyl-N <sup>1</sup> -{(1S, 2R)-	
1-(3,5-	
difluorobenzyl)-3-[(3-	
ethylbenzyl)amino]-2-	
hydroxypropyl}-N <sup>2</sup> -[2-	
(dipropylamino) -2-	
3014 oxoethyl]glycinamide	
g F 3-(4-chlorophenyl)-N <sup>1</sup> -	
((1S,2R)-1-(3,5-	
difluorobenzyl)-3-[(3-	
ethylbenzyl)amino]-2-	
hydroxypropy1}-N <sup>5</sup> , N <sup>5</sup> -	
3015 dipropylpentanediamide	
$\frac{1}{2} (2E) - N^5 - \{(1S, 2R) - 1 - (1S, 2R)$	
(3,5-difluorobenzyl)-	
3-[(3-	-
ethylbenzyl)amino]-2-	
hydroxypropy1}-2-	,
(methoxyimino) -N <sup>1</sup> , N <sup>1</sup> -	
3016 dipropylpentanediamide N <sup>1</sup> -{(1S,2R)-1-(3,5-	
difluorobenzyl)-3-[(3-	
ethylbenzyl)amino]-2-	*
etnylbenzyl)amino]-2- p p hydroxypropyl}-N <sup>2</sup> -[2-	
nydroxypropy1}-N°-[2-	
(dipropylamino) -2-	
oxoethyl]-N²-	
3017 phenylglycinamide	

		,	
	The state of the s	N <sup>1</sup> -{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-N2,N2-	
1	N H OH H	dipropylcyclohexane-	
3018	<u> </u>	1,2-dicarboxamide	
	Н	N-{(15,2R)-1-(3,5-	
	\	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	O / "OH "	hydroxypropyl}-3-	
	)	phenylpropanamide	***467.
	IND F		3
3019			
	<u> </u>	$N^{1}-\{(1S,2R)-1-(3,5-$	
		difluorobenzyl)-3-	
	H. OH H CNHO	[(1,1-dioxido-3,4-	
	H OH H NHO	dihydro-2H-1,2-	
		benzothiazin-4-	
	F T	y1)amino]-2-	
		hydroxypropyl}-5-	
	<u> </u>	methyl-N <sup>3</sup> , N <sup>3</sup> -	
3020	P	dipropylisophthalamide	
	,	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-3-	
	H. OH H -NHO	[(1,1-dioxido-3,4-	
	HH OH H	dihydro-2H-1,2-	
		benzothiazin-4-	
		yl)amino]-2-	
		hydroxypropyl}-5-	
2021	ļ ģ	methyl-N <sup>3</sup> , N <sup>3</sup> -	
3021		dipropylisophthalamide $N^1-\{(1S,2R)-1-(3,5-$	<del> </del>
		difluorobenzyl)-3-	
1		[(2,2-dioxido-3,4-	
}	HH QH H S=O	dihydro-1,2-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	benzoxathiin-4-	_
	F O H ( )	yl)amino]-2-	
1		hydroxypropyl}-5-	
		methyl-N <sup>3</sup> , N <sup>3</sup> -	
3022	ļ Ė	dipropylisophthalamide	
	,	$N^{1}$ - { (1S, 2R) -1 - (3, 5-	
		difluorobenzyl)-3-	
1		[(2,2-dioxido-3,4-	
	H OH H S=O	dihydro-1,2-	
		benzoxathiin-4-	
1	F	y1)amino]-2-	
1		hydroxypropyl}-5-	· .
	Ĭ.	$methyl-N^3, N^3-$	
3023	F	dipropylisophthalamide	

	· · ·	$N^1 - \{ (1s, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-2-	
	T to T	hydroxy-3-[(7-methoxy-	
		1,2,3,4-	
	'' ٹ_ۃ ۃ ا	tetrahydronaphthalen-	i
	F—( )	1-yl)amino]propyl}-5-	
		methyl-N <sup>3</sup> ,N <sup>3</sup> -	
3024	F	dipropylisophthalamide	
	``	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - $	
		difluorobenzyl)-2-	
		hydroxy-3-[(7-methoxy-	
		1,2,3,4-	
1		tetrahydronaphthalen-	
		1-yl)amino]propyl}-5-	
	· 🖳	methyl-N3,N3-	
3025	F	dipropylisophthalamide	
	,,,(¬),	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
	HN N	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-(1H-	**632.3
		$imidazol-2-yl)-N^3, N^3-$	
		dipropylisophthalamide	ł
2006			
3026	F	N-{(1S,2R)-1-(3,5-	· · · · · ·
1	N OH	difluorobenzyl)-3-[(3-	
1		ethylbenzyl)amino]-2-	
	0. 4 1. 4. 4. 4. 4. 4. 4. 4. 4. 4. 4. 4. 4. 4.		**522
		hydroxypropyl}-2-	77544
		propyl-1,3-	j
	ļ Ė	benzoxazole-6-	
3027		carboxamide	
		N-{(1S,2R)-1-(3,5-	
	H OH H	difluorobenzyl)-3-[(3-	l
	N N N	ethylbenzyl)amino]-2-	
	l l l	hydroxypropyl}-2-	**494
		methyl-1,3-	
1	HCI	benzoxazole-6-	
1	<b> </b>	carboxamide	
3028		hydrochloride	
		5-[(tert-	
1	HN	butylamino)sulfonyl]-	
	0=\$=0	$N^{1} - \{ (1s, 2R) - 1 - (3, 5 - 1) \}$	
1	H PH H PH H	difluorobenzyl)-3-[(3-	**701
1	\widetilde\n'\wid	ethylbenzyl)amino]-2-	"" /01
1	0 0 <del>-</del>	hydroxypropyl}-N3,N3-	
1		dipropylisophthalamide	
3029	Ţ		
		5-{[tert-	
1	N.	butyl (methyl) amino] sul	
	o=\$=0	fonyl $\}-N^1-\{(1S,2R)-1-$	
1	H OH H OH H	(3,5-difluorobenzyl)-	
1		3-[(3-	**715
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-N <sup>3</sup> , N <sup>3</sup> -	
2020		dipropylisophthalamide	
3030	<u>                                     </u>	стргоругтвориснаташтов	<u> </u>

		N-{(1S,2R)-1-(3,5-	
	H ÔH H	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	**522
1.		isopropyl-1,3-	
1		benzoxazole-6-	
2021	Ė	carboxamide	
3031	u u	(2S) -N-{ (1S, 2R) -1-	<del></del> -
}	ō, HH ō, H		
		(3,5-difluorobenzyl)-	
}	I I I I I I I	3-[(3-	
1		ethylbenzyl)amino]-2-	
	F-{\_\}	hydroxypropyl}-2-	
İ		hydroxy-2-(1-	
3032	)F	naphthyl)ethanamide	
	OHH OHH	(2R)-N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	N N N N N N N N N N N N N N N N N N N	3-[(3-	
1	📞 " "	ethylbenzyl)amino]-2-	
1	_ /=<	hydroxypropyl}-2-	
1		hydroxy-2-(1-	
3033	F	naphthyl)ethanamide	
5033	F	N-{(1S, 2R) -1-(3, 5-	
	F	difluorobenzy1)-3-[(3-	
	1 ( )	ethylbenzyl)amino]-2-	
		hydroxypropyl}isonicot	
	l Ö (H	inamide	}
		inamide	
	N H H OHH		
3034	N H OH		
	<i>_</i> ↑.	$N^1$ -{(1S,2R)-1-benzyl-	
	O N	3-[(3-	ļ
	н он н	ethylbenzyl)amino]-2-	
		hydroxypropyl}-N3-	**569.3
		methy1-5-(1,3-oxazo1-	
ŀ		$[2-y1)-N^3-$	
3035		propylisophthalamide	
	<i>√</i> √.		l .
	o √ 'n		
1	, OH O		
			**642.3
· ·			042.3
3036	Ė Ė		ļ
	O. N	,	
1	ľ	1	
	I № н Бн й В		
			**614.4
1	0 0 ± F H		
3037	Ţ		
<u> </u>		<u> </u>	

3038	DH HN F	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-[1- (ethoxymethyl)-1H- imidazol-2-yl]-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	**690.3
3039	OH H N HCI	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-propyl-1,3-benzoxazole-5-carboxamidehydrochloride	**522
3040	HOH HOLL HOLL HOLL HOLL HOLL HOLL HOLL	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-isopropyl-1,3-benzoxazole-5-carboxamidehydrochloride	**522
3041	O S O H O H N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[ethyl(methyl)amino]sulfonyl}benzamide	**560
3042	H QH H H N N HCI	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-1,3-benzoxazole-5-carboxamidehydrochloride	**494
3043	O S = O H OH H N N F F	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(methylsulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	**644

3044	HCI PHCI	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(methylsulfonyl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamidehydrochloride	**645.0 · 4
3045	N O H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-1,3-benzoxazole-7-carboxamidehydrochloride	**494
3046	O O H N N N N N N N N N N N N N N N N N	methyl 3-[({(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]benzoate	**497.3
3047	HN N F	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(5-methoxy- 1,2,3,4- tetrahydronaphthalen- 1-yl)amino]propyl}-5- methyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3048	H OH H	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(5-methoxy- 1,2,3,4- tetrahydronaphthalen- 1-yl)amino]propyl}-5- methyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3049	HO HON H	ELAN-91970	

	H OH H N	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzy1)-2- hydroxy-3-[(6-methoxy- 1,2,3,4- tetrahydronaphthalen- 1-y1)amino]propy1}-5-	
3050		methyl-N³,N³- dipropylisophthalamide	
3051	N OH H N N N	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(1S)-2,3-dihydro-1H- inden-1-ylamino]-2- hydroxypropyl}-5- methyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3052	N O O N H OH H	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>2</sup> ,N <sup>2</sup> - dipropylcyclohexane- 1,2-dicarboxamide	,
3053		N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}benzamide	**616
	H H H N H H N H H N H H N H H N H N H N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[ethyl(methyl)amino]sulfonyl}benzamide	* <b>*</b> 560
3055	N S HOOOH	formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[ethyl(methyl)amino]sulfonyl}benzamide(1:1)	***560. 1

	<del></del>	·	
		N-{(1s,2R)-1-(3,5-	
	H'O'H	difluorobenzy1)-3-[(3-	
-		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-3,5-	
1	0 -	dimethylbenzamide	
Ì			
3056	F		
	Ę	$N^{1}$ -butyl- $N^{3}$ -((1S,2R)-1-	
		(3,5÷difluorobenzyl)-	
	F	3-{[1-(3-	
1		ethynylphenyl)cyclopro	
	N N N N N N N N N N N N N N N N N N N	pyl]amino}-2-	
	H HOH H	hydroxypropyl)-N <sup>1</sup> -	
		methyl-5-(1,3-thiazol-	
3057	\ \\\s	2-y1) isophthalamide	
3037		$N^{1}$ -buty1- $N^{5}$ -{ (1S, 2R)-1-	
	<u>[</u>		
		(3,5-difluorobenzyl)-	
	0 0 7	3-[(3-	
	N N N N N N N N N N N N N N N N N N N	ethylbenzyl)amino]-2-	
3050	T HAOHH	hydroxypropyl}-N¹-	
3058		methylpentanediamide	
	Ţ	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
1		difluorobenzyl)-3-[(3-	
1	Q Q (H	ethylbenzyl)amino]-2-	
	N N N N N N N N N N N N N N N N N N N	hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup>	
	H OH H	dipropylpentanediamide	
3059	Ĭ		
	F	$(2R)-N^5-\{(1S,2R)-1-$	
		(3,5-difluorobenzyl)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	
	N S N H IN N	hydroxypropyl}-2-	
	H, H OH H	methyl-N <sup>1</sup> , N <sup>1</sup> -	
3060		dipropylpentanediamide	
	F	$(2S) - N^5 - \{ (1S, 2R) - 1 -$	
		(3,5-difluorobenzyl)-	
		3-[(3-	
	P P (H→ F	ethylbenzyl)amino]-2-	
		hydroxypropy1}-2-	
	H OH H	methyl-N <sup>1</sup> , N <sup>1</sup> -	
3061		dipropylpentanediamide	
	Ę Ę	N <sup>1</sup> -{(1s, 2r) -1-(3,5-	
		difluorobenzyl)-3-[(3-	
]		ethylbenzyl)amino]-2-	
	I SHOW F	hydroxypropyl}-N <sup>4</sup> -	
L		dipropylsuccinamide	
3062	о н он н		
I	, F	N <sup>1</sup> -{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	人。。人人。	ethylbenzyl)amino]-2-	
1		hydroxypropyl}-N2-[2-	
]		(dipropylamino)-2-	
1	□ OH " U	oxoethyl]-N <sup>2</sup> -	
3063	<u> </u>	methylglycinamide	
		<u> </u>	

		$N^{1} - \{ (1s, 2R) - 1 - (3, 5 - 1) \}$	l
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
İ		hydroxypropyl}-N2-[2-	j
	N N N N N N N N N N N N N N N N N N N	(dipropylamino) -2-	,
1	H OH H	oxoethyl]glycinamide	
3064			
	F	$N-\{(1S,2R)-1-(3,5-$	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-[2-	
	N N N N N N N N N N N N N N N N N N N	(methoxymethyl)pyrroli	
	H OH'H		
	1	din-1-y1]-5-	
3065	δ	oxopentanamide	
	[	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - $	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-N <sup>5</sup> -(2-	
	I NY Y NY TINH WY YYYY	furylmethyl)-N <sup>5</sup> -	
	∵ он ′′ 🗸	methylpentanediamide	
3066	<u>Ló</u>		
	Į Ę	$N^{1} - ((1S, 2R) - 1 - (3, 5 -$	
1		difluorobenzyl)-3-	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	{[(4-ethylpyridin-2-	
1		yl)methyl]amino}-2-	
		hydroxypropyl)-5-	
	N H H CH H	methyl-N <sup>3</sup> , N <sup>3</sup> -	
	/ Митон и М	dipropylisophthalamide	
2067		dipropyrisophicharamice	
3067		N <sup>4</sup> -((1S, 2R)-1-(3,5-	
1	Ę	difluorobenzyl)-3-{[1-	
1		(3-	
	F	ethynylphenyl)cyclopro	
		pyl]amino}-2-	
	N N N N N N N N N N N N N N N N N N N	hydroxypropyl)-6-	
	I NOH TOH TOH TOH TOH TOH TOH TOH TOH TOH T	$methyl-N^2, N^2-$	
		dipropylpyridine-2,4-	
3068		dicarboxamide	
7000	<del>                                     </del>	N-{(1s,2r)-1-(3,5-	
	$\times_{\alpha}$		
-	Υ · ·	difluorobenzyl)-3-[(3-	
	OH	ethylbenzyl)amino]-2-	
1	H PH H	hydroxypropy1}-2,2-	
		dimethylchromane-7-	**523
		carboxamide	
	YY'	hydrochloride	
	HCI	_	
	) HCI		
3069	F		
	H OH H	$N-\{(1S,2R)-1-(3,5-$	
		difluorobenzyl)-3-[(3-	
	1 ~ ~ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\	ethylbenzyl)amino]-2-	, , <b>-</b>
1	Ö	hydroxypropyl}-2,2-	**523
	11 1		l
		dimethylchromane-o-	
3070		dimethylchromane-6- carboxamide	

•			
3071	H QH H N N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-1,3-benzoxazole-4-carboxamidehydrochloride	**494
3072		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-propyl-1,3-benzoxazole-4-carboxamidehydrochloride	
3073	H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}benzamide	**616
3074	HO-S-OHOH  HO-S-OHOH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{dihydroxy[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-lambda4-sulfanyl}benzamide	**602
3075	N O H O F	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-6-carboxamide	**534
3076	H OH H N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-propyl-1H-indole-6-carboxamide	**520

		1-butyl-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1H- indole-5-carboxamide hydrochloride	**534
3077	Ö F HCI		
		N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[4-(2-hydroxyethyl)-1,3-oxazol-2-yl]benzamide	**550.3
3078	F		
3079		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamide	**663.3
3080	SN H QH H N N F Ha	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropyl-5-(1,3-thiazol-2-yl)isophthalamidehydrochloride	**663.3
3081	D D D D D D D D D D D D D D D D D D D	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-([(4-ethylpyridin-2-yl)methyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
	F F N H N H N H N H N H N H N H N H N H	N-((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)-4- (ethoxymethyl)benzamid	
3082		e	<u></u>

3083	H OH H N HCI	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}indoline-6-carboxamidehydrochloride	**535.9
3084	HN-S=O HN	3-[(tert-butylamino)sulfonyl]- N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide	**574
3085	O H OH H HCI	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,3-dihydro-1,4-benzodioxine-6-carboxamidehydrochloride	
3086	OH O=S=O HN OFF	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]sulfonyl}benzamide	**602
3087	H-Cl <sub>H-Cl</sub>	N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N³,N³-dipropyl-5-pyridin-4-ylisophthalamidedihydrochloride	**643.3
3088	H OH H H H CI	N <sup>1</sup> -butyl-N <sup>3</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-N <sup>1</sup> ,5-dimethylisophthalamidehydrochloride	*561

3089	H-CI DH HZ F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamidehydrochloride	**608.3
3090	H-CI H-CI H-N P H-CI H-N P F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl)amino]-2-hydroxypropyl}-3-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylbenzamidehydrochloride	**590.3
3091	OH H	3-(1-butyl-1H-pyrazol- 4-yl)-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}propanam ide	
3092	H-CI H-QI H H N N F	N-((1S,2R)-1-(3,5-difluorobenzy1)-3-{[1-(3-ethylpheny1)cyclopropy1]amino}-2-hydroxypropy1)-3-{[(2R)-2-(methoxymethy1)pyrrolidin-1-y1]carbony1}-5-methylbenzamidehydrochloride	**620.3
3093	H OH H N N N N N N N N N N N N N N N N N	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indazole-6-carboxamide	
3094	S H QH H N F F F	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-thien-2-yl-1,3-thiazole-4-carboxamide	**** 528.2 (+)
3095	H <sub>2</sub> N-N N F F	5-(aminosulfonyl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-1H-pyrrole-2- carboxamide	**** 521.2 (+)

			<del></del>
	_	N-{(1s,2R)-1-(3,5-	
	/ 11 - 11 - 11	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	****
	0=S=0 0 F	hydroxypropyl}-2-{[(2-	604.1
		furylmethyl)sulfonyl]m	(+)
1	Y Y	ethyl}-1,3-thiazole-4-	i
3096	F	carboxamide	
		N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	1 - 05~ H *'' H 1	ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-{[(4-	
1		fluorobenzyl)sulfonyl]	
1	<b> </b>		
	F	methyl}-1,3-thiazole-	
3097		4-carboxamide	
1		1-butyl-N-{(1S,2R)-1-	
	N <sub>2</sub> O	(3,5-difluorobenzyl)-	
		3-[(3-	
	l [ ] H OH H [ ]	ethylbenzyl)amino]-2-	
	N N N N N N N N N N N N N N N N N N N	hydroxypropyl}-4-	**640.8
		[methyl(methylsulfonyl	
		)amino]-1H-indole-6-	
		carboxamide	
3098	F		
	<b>E</b>	N-((1S,2R)-1-(3,5-	
	1	difluorobenzyl)-3-{[1-	Ì
		(3-	
	Ŷ MH ▽	ethynylphenyl)cyclopro	
1		pyl]amino}-2-	
	н нон н	hydroxypropyl)-4-(2-	
3099	0 0	methoxyethyl) benzamide	
		$N^{1}$ -butyl- $N^{3}$ -{ (1S, 2R)-1-	
	N <sub>V</sub> S	(3,5-difluorobenzyl)-	
		2-hydroxy-3-[(1-	
		phenylcyclopropyl)amin	,
1	N N N N N N N N N N N N N N N N N N N	o]propyl}-N <sup>1</sup> -methyl-5-	
		(1,3-thiazol-2-	
1		yl)isophthalamide	
1		A T \ TBODILCHGTGHTGE	
2100	<u></u>		
3100	F · · ·	N <sup>1</sup> -{(1S,2R)-1-(3,5-	<u> </u>
	N_ \dot \dot \dot \dot \dot \dot \dot \dot	difluorobenzyl)-2-	
		1 -	
	l \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	hydroxy-3-[(1-	
		phenylcyclopropyl)amin	
		o]propyl}-5-(1,3-	
		$oxazol-2-yl)-N^3, N^3-$	
,		dipropylisophthalamide	1
	\ <del>\</del> _ <del>-</del> F		
3101			
2404	<u> </u>	<u> </u>	<u> </u>

3102	HN OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(ethylamino)sulfonyl]benzamide	**546
		N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-[(methylamino)sulfonyl]benzamide	**532
3104	N OH H	(2E) -3-(1-buty1-1H- pyrazo1-4-y1)-N- {(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}prop-2- enamide or (2E)-3-(1- buty1-1H-pyrazo1-4- y1)-N-{(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}prop-2- enamide	
3105		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isoquinoline-7-carboxamidedihydrochloride	**490.1
3106	H DH H CI H CI H CI H CI	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamidedihydrochlorideorN-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(propylamino)isoquinoline-7-carboxamidedihydrochloride	**547.3

3107	DE LA COMPANIA DEL COMPANIA DEL COMPANIA DE LA COMP	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-{[(2-hydroxy-1,1-dimethylethyl)amino]sulfonyl}-N <sup>3</sup> , N <sup>3</sup> -dipropylisophthalamide	**730.8
3108	O N	methyl 3-(2-{3- [({(1s,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}amino)ca rbonyl]phenyl}-1,3- oxazol-5-yl)propanoate	**591.9
3109	HO-Q N HO-Q HO-	3-(2-{3-[({(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]phenyl}-1,3-oxazol-5-yl)propanoicacid	**578.2
3110	HO N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(3-hydroxypropyl)-1H-indole-6-carboxamide	**536.8
3111	PHH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-ethoxybenzamide	
3112	F O H N H H H OH H	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-6-(pyrrolidin-1-ylcarbonyl)isonicotinamide	

2112	P P P P P P P P P P P P P P P P P P P	N <sup>1</sup> -((1S,2R)-1-(3,5- difluorobenzyl)-3- {[(6-ethylpyridin-2- yl)methyl]amino}-2- hydroxypropyl)-5- methyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3113		N-{(1S,2R)-1-(3,5-	
3114	F	difluorobenzyl) -3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(dipropylamino)sulfonyl]benzamide	
	F	N <sup>1</sup> -((1S,2R)-1-(3,5-	
3115	F F	difluorobenzyl)-3- {[(6-ethylpyridin-2- yl)methyl]amino}-2- hydroxypropyl)-5-(1,3- oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
		tert-butyl (1R)-1-	
3116	O O O H H N N N N N N N N N N N N N N N	<pre>[({(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}amino)ca rbonyl]-3- (methylsulfinyl)propyl carbamate</pre>	**** 582.1 (+)
3117	N OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)isonicotinamide or ELAN154894	-
3118	N OH H N HO	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- (dipropylamino)isonico tinamide hydrochloride	**539.3
3119	O O O O O O O O O O O O O O O O O O O	(2R)-2-amino-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4- (methylsulfinyl)butana mide	**** 482.2 (+)

3120	O S O H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[ethyl(methyl)amino]sulfonyl}-5-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}benzamide	**701
3121	DH HZ F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[methyl(propyl)amino]isoquinoline-7-carboxamide or N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[methyl(propyl)amino]isoquinoline-7-carboxamide	**561.4
3122	OH HAN F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)benzamide	**506.2
3123	F F Br	N <sup>1</sup> -[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
3124	F F Br H HOH HGI	N <sup>1</sup> -[(1S,2R)-3-{[1-(3-bromophenyl)cyclopropyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamidehydrochloride	**709.2 + 711.2
3125	P N-NH H OH H	N <sup>5</sup> -{(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}-N <sup>3</sup> ,N <sup>3</sup> - dipropy1-1H-pyrazole- 3,5-dicarboxamide	·

	F	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-3-[(3-	ļ
	0 0 1 F	ethylbenzyl)amino]-2-	•
		hydroxypropyl \ -N2, N2-	
		dipropylcyclobutane-	
3126		1,2-dicarboxamide	
	F	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-	
		[(dipropylamino)carbon	
2127	I O H OH H W	1	
3127		othioyl]benzamide	
	=	3-[(E)-	
		(cyanoimino) (dipropyla	
		mino)methyl]-N-	
	N <sup>CN</sup> O CF	{ (1s,2R) -1- (3,5-	
		difluorobenzyl)-3-[(3-	
	Г Д Н ОН Н Г Д	ethylbenzyl)amino]-2-	
1		hydroxypropyl}benzamid	
3128		le l	
	. ,	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-2-	
İ	HH OH H	hydroxy-3-[(6-	
		isopropyl-2,2-dioxido-	
		3,4-dihydro-1H-	
	ÖĪ	isothiochromen-4-	
1	0,0		•
		y1)amino]propy1}-5-	
		methyl-N <sup>3</sup> , N <sup>3</sup> -	
3129	·	dipropylisophthalamide	
İ	L	N-{(1s,2r)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	. 0	hydroxypropyl}-3-(1-	
	<b>/ &gt;</b> −F	propylbutoxy)benzamide	
3130	<u>}</u> =/	·	
3130	F F	N <sup>1</sup> -((1S,2R)-1-(3,5-	
	<u> </u>	1	
	1 PL-	difluorobenzyl)-3-	'
1	0 0	{[(5-ethylpyridin-3-	"
		yl)methyl]amino}-2-	
		hydroxypropyl)-5-(1,3-	
		$oxazol-2-yl)-N^3,N^3-$	
	' N O	dipropylisophthalamide	· ·
3131		<u> </u>	
		$N^{1}-\{(1S,2R)-1-(3,5-$	
1	Y	difluorobenzyl)-2-	
	HH OH H	hydroxy-3-[(6-	
	N N N N N N N N N N N N N N N N N N N	isopropyl-2,2-dioxido-	
		3,4-dihydro-1H-	
		isothiochromen-4-	
1	0 0	yl)amino]propyl}-5-	ļ
1		methyl-N <sup>3</sup> , N <sup>3</sup> -	
2122	`F	dipropylisophthalamide	
3132	<u></u>	drbiobArraobucugramide	L

		, <u>, , , , , , , , , , , , , , , , , , </u>	
3133		N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1-(2- methoxyethyl)-1H- indole-6-carboxamide	**536
3134	ON HOLL HOLL F	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3,4- dihydro-2H-1,4- benzoxazine-6- carboxamide hydrochloride	**496
3135		N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2s)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]sulfonyl}benzamide	**757
3136	S O H H N H N H H N H H N H H N H H N H H N H H N H H N H H N H H N H H N H H N H H N H N H H N H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-thiazol-2-yl)benzamide	**522.2
3137	H H N F	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4,8-diethoxyquinoline-2-carboxamide	**** 578.3 (+)
3138	O N O H O F H CI H CI	2-(4-butyl-3- oxopiperazin-1-yl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e dihydrochloride	
3139	S P P P P P P P P P P P P P P P P P P P	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> -[2-(dimethylamino)ethyl]-N <sup>3</sup> ,5-dimethylisophthalamide	

3140		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methylbutandyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	·
3141	F O N H H O H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(4-methylpentanoyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	,
	F O N H O H	isobutyl (2R,3S)-4- (3,5-difluorophenyl)- 3-({3- [(dipropylamino)carbon y1]-5- methylbenzoyl}amino)- 2-	
3142		hydroxybutylcarbamate	
	F O O O O O O O O O O O O O O O O O O O	ethyl (2R,3S)-4-(3,5-difluorophenyl)-3-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)-2-	
3143		hydroxybutylcarbamate	
3144	O O H N N N H HOH H	N <sup>1</sup> -[(1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(pyrimidin-2-ylamino)propyl]-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
3145	H N H H OH H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> -[(1S)-1-methylpropyl]isophthalamide	
3146	H O O H H HOH H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-N <sup>3</sup> -[(1R)-1-methylpropyl]isophthalamide	

		N-{(1S,2R)-1-(3,5-	
	N OH	difluorobenzyl)-3-[(3-	
	1 1 1 1 1 1 1 1 1	ethylbenzyl)amino]-2-	
		hydroxypropy1}-2-	**554.4
	0 ~ F '	(dipropylamino)-6-	331.1
	Ĭ	methylpyrimidine-4-	
3147	F	carboxamide	
		1-	
		[butyl(methyl)amino]-	
	,	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	OH	ethylbenzyl)amino]-2-	ļ
		hydroxypropyl}isoquino	
	"\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	line-7-carboxamide or	l
	N 0 T	1-	**575.4
		[butyl (methyl) amino] -	
	Ţ		
	· · · · · · · · · · · · · · · · · · ·	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	1
		ethylbenzyl)amino]-2-	
		hydroxypropyl}isoquino	
3148		line-7-carboxamide	
		N-{(1s,2R)-1-(3,5-	,
	н он н	difluorobenzyl)-3-[(3-	·
		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-1,3-	
	0 ~ F '	dihydro-2-	**529
	HCI	benzothiophene-5-	
		carboxamide 2,2-	
3149	F	dioxide hydrochloride	
3149			
}		N-((1S,2R)-1-(3,5-	
1	Ę	difluorobenzyl)-3-{[1-	
		(3-	
	F	ethynylphenyl)cyclopro	
		pyl]amino}-2-	
	N N N N N N N N N N N N N N N N N N N	hydroxypropyl)-3-	
	Н нон н	{ [ (2R) -2-	
1	~	(methoxymethyl)pyrroli	
1	\ \	din-1-yl]carbonyl}-5-	
3150		methylbenzamide	
		N-((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-{[1-	
1	F	(3-	
1	T <sub>F</sub>	ethynylphenyl)cyclopro	
İ		pyl]amino}-2-	
	KN TY HAT HIT	hydroxypropyl)-3-	
	1	{[(2R)-2-	
1	Q '	(methoxymethyl)pyrroli	
	F^_	din-1-yl]carbonyl}-5-	
	ļ	methylbenzamide	
3151	]	trifluoroacetate	<u> </u>
	н он н	$N-\{(1S,2R)-1-(3,5-$	
1		difluorobenzyl)-3-[(3-	
	N ~ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	ethylbenzyl)amino]-2-	
	0 \$\sqrt{F}	hydroxypropyl}-1-	**534.2
2150	<b>Y</b>	isobutyl-1H-indole-6-	
3152	<u> </u>	carboxamide	<u></u>

		carboxamide	<u></u>
3153	H H N F F	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1H-indole-6-carboxamide	**627.8 6
3154	H OH H N N F F	1-butyl-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4- methyl-1H-indole-6- carboxamide	**548.9 4
3155	H OH H N HCI	N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-3-oxo-2-propy1-2,3-dihydro-1,2-benzisothiazole-6-carboxamide 1,1-dioxide hydrochloride	**586
3156	H OH H N N N N N N N N N N N N N N N N N	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(1,3-oxazol-2-yl)-1H-indole-6-carboxamide	**601.9 9
3157	H OH H N	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-methylisonicotinamide	**553
3158	S H QH H N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(methylsulfonyl)methyl]-1,3-thiazole-4-carboxamide	**** (537.8) (+)
3159	NH <sub>2</sub> H OH H N H CI F	4-amino-1-butyl-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1H- indole-6-carboxamide hydrochloride	

		$N-\{(1S, 2R)-1-(3, 5-$	
	Q	difluorobenzyl)-3-[(3-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	ethylbenzyl)amino]-2-	
i		1	
		hydroxypropyl}-2-	
	0 0 to 1	ethy1-3-oxo-2,3-	
	T Y	dihydro-1,2-	
	на на	benzisothiazole-6-	
•	Į E	carboxamide 1,1-	
3160	•	dioxide hydrochloride	
3.00		3-[(tert-	
	1	butylamino)sulfonyl]-	
	HN		
	0=\$=0	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	ŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢŢ	ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-	
		{[(2S)-2-	
	I I	(methoxymethyl)pyrroli	
		din-1-	
2161	Ė	yl]carbonyl}benzamide	
3161			
		3-{[(2S)-2-	
		butylpyrrolidin-1-	
1	H OH H	yl]carbonyl}-N-	
		{ (1s,2R)-1-(3,5-	
	<b>~</b>	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-	
3162	 	methylbenzamide	
2102			
		4-butyl-N-{(1S,2R)-1-	•
	н Он н	(3,5-difluorobenzy1)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3,4-	
		dihydro-2H-1,4-	
	ľ	benzoxazine-6-	
3163	F	carboxamide	
F-03		N-{(1S,2R)-1-(3,5-	
		• • • • • • • • • • • • • • • • • • • •	
		difluorobenzyl)-3-[(3-	
4	, OH ,	ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-	
		methyl-5-{[(2R)-2-	
	H-CI	(propoxymethyl)pyrroli	
	Y	din-1-	
	ļ F	yl]carbonyl}benzamide	
3164		hydrochloride	*
7101		2-(1-buty1-2-	
	H QH H	oxopiperidin-4-yl)-N-	
		{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	VNV U YNF	ethylbenzyl)amino]-2-	
		hydroxypropyl}acetamid	
3165	I	e	
2103	<u> </u>	<u>r</u>	L

<del></del>			
	<u></u>	N-{(1S,2R)-1-(3,5-	
	L L F	difluorobenzyl)-3-[(3-	
	Q (₃H	ethylbenzyl)amino]-2-	İ
	NO NO NO NO NO NO NO NO NO NO NO NO NO N	hydroxypropyl}-3- pentylbenzamide	
3166	H H OH H		
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	l wh	ethylbenzyl)amino]-2-	
L		hydroxypropyl}-3-(2-	
3167	J HHOH H J	ethylhexyl)benzamide	
	F	ethyl 5-{3-[({(1s,2R)-	
		1-(3,5-	
	↓ F	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	H H OH H	hydroxypropyl amino) ca	
3168	₩ы он	rbonyl]phenyl}-2- furoate	
	Ę	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	F	ethylbenzyl)amino]-2-	
	P (JH	hydroxypropyl}-1,1'-	
		biphenyl-3-carboxamide	·
3169	H H OH H C		
	Ę	N-{(1S,2R)-1-(3,5-	
1		difluorobenzyl)-3-[(3-	
	□ PF	ethylbenzyl)amino]-2-	
		hydroxypropyl}-2'-	
2170	S T HOH H T	(methylthio) -1,1'-	
3170	SOH	bipheny1-3-carboxamide	<u> </u>
	<u> </u>	N-{(1S,2R)-1-(3,5-	
	L F	difluorobenzyl)-3-[(3-	
	F O NH	ethylbenzyl)amino]-2- hydroxypropyl}-3-(2-	
		fluorobenzyl)benzamide	
3171	O D HHOH H D	22do103cm2y1/Ben2amitde	
		N-{(1S,2R)-1-(3,5-	
}		difluorobenzy1)-3-[(3-	
	,,	ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-(4-	
3172	TO THANK TO	fluorobenzyl)benzamide	
	Ę	ethy1 3'-[({(1S,2R)-1-	<del></del>
		(3,5-difluorobenzyl)-	
	∫ F	3-[(3-	
	I NH	ethylbenzyl)amino]-2-	
	I Y Y N N N N N N N N N N N N N N N N N	hydroxypropyl}amino)ca	
	HHOH H	rbonyl]-1,1'-biphenyl-	}
3173		2-carboxylate	
	Ę	N-{(1S,2R)-1-(3,5-	
	F	difluorobenzyl)-3-[(3-	ľ
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3',5'-	
2174	H H OH H	difluoro-1,1'-	
3174	L V VIII VIII V	biphenyl-3-carboxamide	

		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	
	166 3 11 4	phenylacetamide	1
		phenyracecamice	]
	HHALL H	1	
	н н он н		ł
3175			
5175	Ę	tert-butyl 4-	
		[({(1s,2r)-1-(3,5-	
	F	difluorobenzyl)-3-[(3-	
	P (H		
		ethylbenzyl)amino]-2-	
	O N HHOH H	hydroxypropyl}amino)ca	
3176		rbonyl]benzylcarbamate	
	·F	(2R)-N-{(1S,2R)-1-	
1	<u> </u>	(3,5-difluorobenzyl)-	
		3-[(3-	
1			
1	P (JH	ethylbenzyl)amino]-2-	
	人人人人人人人人	hydroxypropyl}-2-	
	HOTH H HOH H	hydroxy-2-	
3177	н и пон и	phenylethanamide	
	Ę	(2S) -N-{(1S,2R)-1-	
}		(3,5-difluorobenzyl)-	'
		3-[(3-	
	F F	ethylbenzyl)amino]-2-	
	I N	hydroxypropyl}-2-	
		<u> </u>	
	H, OH H H, OH H	hydroxy-2-	
3178	W ON WHOM W	phenylethanamide	
	- F	3-(5-chloropentyl)-N-	
		{(1s,2R)-1-(3,5-	
1	CI	difluorobenzyl)-3-[(3-	
	l mH	ethylbenzyl)amino]-2-	ł
		hydroxypropyl}benzamid	
		e	
3179	H H OH H		ļ
1	F F -	N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
1	→ F	ethylbenzyl)amino]-2-	
	§ 0 (HOH	hydroxypropyl}-3-(1-	
1		phenylethyl) benzamide	·
3180	H H OH H	trifluoroacetate	[
<del></del>	F F	3-(cyclohexylmethyl)-	<del> </del>
1	1	N-{(1S, 2R) -1-(3,5-	
			1
		difluorobenzyl) -3-[(3-	
1	P (MH	ethylbenzyl)amino]-2-	
		hydroxypropyl}benzamid	
3181		е	
7101	H OH	3-cyclopentyl-N-	<del> </del> -
1	<u> </u>		
		{(1s, 2r) -1 - (3,5-	
	J≈ F	difluorobenzyl)-3-[(3-	,
	MH (mH	ethylbenzyl)amino]-2-	
		hydroxypropyl}benzamid	
3182	I N H OH H	e	
2102			<u> </u>

	<b>\</b>	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	F	ethylbenzyl)amino]-2-	
1	° ( <sub>M</sub> H	hydroxypropyl}-3-hex-	
	しっる人だんふる	5-enylbenzamide	
3183	THHOH T	_	
	ļ <u>.</u> . Ę	3-(6-cyanohexyl)-N-	
Ì		{(1s,2R)-1-(3,5-	
İ	F F	difluorobenzyl)-3-[(3-	
	P (ωH	ethylbenzyl)amino]-2-	
		hydroxypropyl}benzamid	
3184	H H OH H	e	
		N <sup>1</sup> -((1s,2R)-1-(3,5-	
		difluorobenzyl)-3-{[3-	
	L\F	(2-formylthien-3-	
	9 P H	y1)benzyl]amino}-2-	
1		hydroxypropyl)-5-	
		methyl-N <sup>3</sup> , N <sup>3</sup> -	
3185		dipropylisophthalamide	
	F	N <sup>1</sup> -((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-{[3-	
		(5-formylthien-3-	
		yl)benzyl]amino}-2-	
•		hydroxypropyl)-5-	
	I A HOH.	methyl-N <sup>3</sup> , N <sup>3</sup> -	·
3186	' '	dipropylisophthalamide	
		$N^{1}$ - ((1S, 2R) -1 - (3, 5-	
	<b>₹</b>	difluorobenzyl)-2-	
		hydroxy-3-{[3-(6-	
		methoxypyridin-2-	
ĺ			
	HANH U	yl)benzyl]amino}propyl	
	T	)-5-methyl-N <sup>3</sup> , N <sup>3</sup> -	
3187		dipropylisophthalamide	
	Ę	$N^{1} - [(1S, 2R) - 3 - \{[3 - (5 -$	
•		cyanopyridin-3-	
	F	y1)benzyl]amino}-1-	
		(3,5-difluorobenzyl)-	
	\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\	2-hydroxypropyl]-5-	
	H OH T	methyl-N3,N3-	
3188		dipropylisophthalamide	
		N <sup>1</sup> -((1S,2R)-1-(3,5-	
1		difluorobenzyl)-3-{[3-	
	[L	(6-fluoropyridin-3-	
		yl)benzyl]amino}-2-	
		hydroxypropyl)-5-	
	\	methyl-N <sup>3</sup> , N <sup>3</sup> -	
3189	For I	dipropylisophthalamide	
	<del></del>	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
}	<u></u>	difluorobenzyl)-2-	
		hydroxy-3-[(3-	
	0 0 11 F	pyrimidin-4-	
		F -	
		ylbenzyl)amino]propyl}	
2100		-5-methyl-N <sup>3</sup> , N <sup>3</sup> -	
3190		dipropylisophthalamide	<u> </u>

	E	$N^{1}$ -((1s,2R)-1-(3,5-	
	<b>)</b>	difluorobenzy1)-3-{[3-	
	F	(5-ethylpyrimidin-2-	
	P P (NH N)	yl)benzyl]amino}-2-	
	/	hydroxypropyl)-5-	
	/ " H OH" W	methyl-N3, N3-	
3191	1	dipropylisophthalamide	j
3434		$N^{1} - \{(1S, 2R) - 1 - (3, 5 - 1)\}$	
	<u> </u>	difluorobenzyl)-2-	
		hydroxy-3-[(3-	
ļ	N N	pyrimidin-2-	
		ylbenzyl)amino]propyl}	
		-5-methyl-N <sup>3</sup> , N <sup>3</sup> -	
<u> </u>			
3192		dipropylisophthalamide	
	F	methyl 2-[({(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
		3-[(3-	
	l γ γ γ γ γ γ γ γ γ γ γ γ γ γ γ γ γ γ γ	ethylbenzyl)amino]-2-	
	N N N N	hydroxypropyl}amino)ca	
	и н н онн	rbonyl]-6-	
3193		methylisonicotinate	
	F	$N^4 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
	. <i>[</i> ]	difluorobenzyl)-3-[(3-	i
		ethylbenzyl)amino]-2-	· .
	. β <b>(</b> <sup>1</sup> h	hydroxypropyl}-6-	
		$methyl-N^2, N^2-$	,
	H H OHH	dipropylpyridine-2,4-	
3194		dicarboxamide 1-oxide	Ĺ
F	T N	1-butyl-4-cyano-N-	
	l W	$\{(1s, 2R) - 1 - (3, 5 -$	
		difluorobenzyl)-3-[(3-	
	H QH H	ethylbenzyl)amino]-2-	
		hydroxypropyl}-1H-	1
		indole-6-carboxamide	
ł			
3195	Ė Ė		
	No.	1-butyl-4-cyano-N-	. ,
		{ (1s,2R)-1-(3,5-	
	H QH H	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-1H-	
		indole-6-carboxamide	
1		hydrochloride	
	Ţ		
h100			
3196	HC	5-(diethylamino)-N1-	<del> </del>
		$\{(1S, 2R) - 1 - (3, 5 - 1)\}$	
1	Q Q H F	difluorobenzyl)-3-[(3-	,
	I N N N N N N N N N N N N N N N N N N N	ethylbenzyl)amino]-2-	
	/ W H OH H	hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -	
	l N	dipropylisophthalamide	,
3197			<u> </u>
		-	

'	Ī	N <sup>1</sup> -[(1s,2R)-3-{[3-	
		(diethylamino)benzyl]a	
	9 9 (*****F	mino}-1-(3,5-	
		difluorobenzyl)-2-	
		hydroxypropy1]-5-(1,3-	
1		oxazol-2-yl)- $N^3$ , $N^3$ -	
h100	, N <sub>2</sub>	_	
3198		dipropylisophthalamide	
	5	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - $	
		difluorobenzyl)-3-[(3-	
	0 0 \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-	
		(dimethylamino) -N3, N3-	
	/ " OH " 🗸	dipropylisophthalamide	
3199	' N	dipropyrisophenaramide	
	F.	N <sup>1</sup> -((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	( L-	{[(2-ethylpyridin-4-	
	ુ ુમ		
1		yl)methyl]amino}-2-	
	H HOH H	hydroxypropyl)-5-(1,3-	
		$oxazo1-2-y1)-N^3,N^3-$	
		dipropylisophthalamide	
3200	N N		
2200		N <sup>2</sup> -(tert-	
		butoxycarbonyl)-N <sup>1</sup> -	
<b>∤</b> ;	I то № н о Н н 🔷	,	
1		{ (1s, 2R) -1- (3, 5-	
1	10 N 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	difluorobenzyl)-3-[(3-	
	)	ethylbenzyl)amino]-2-	
	<b>_</b>	hydroxypropyl}-L-	
	( <u> </u>	norleucinamide	
3201			
5201	F	N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	·
	) ~ F	hydroxypropyl}-3-[(3H-	
1		[1,2,3]triazolo[4,5-	
1	Ţ	b]pyridin-3-	
3202	ļ	yloxy) methyl] benzamide	į
F		N-{ (1s, 2r) -1- (3, 5-	
1			
1	OH 1	difluorobenzyl)-2	
1	I С п № н С п	hydroxy-3-[(3-	
1		iodobenzyl)amino]propy	
1		1}-3-{[(2-	
1	YY'	hydroxyethyl) (propyl)a	
	H—CI	mino]methy1}-5-	
	¦ н—а	methylbenzamide	
3203		dihydrochloride	
5203		N-{(1s,2r)-1-(3,5-	
	No.		
	1	difluorobenzyl)-2-	
	H OH H	hydroxy-3-[(3-	
		<pre>iodobenzyl)amino]propy</pre>	
	L ~ ~ ~ I I ~ ~ ~ 1	1}-3-	
1		{[ethyl(propyl)amino]m	
		ethyl)-5-	,
	<u> </u> н—сі	methylbenzamide	ľ
1		mar mirrogramina	
3204	'	dihydrochloride	, ,

3205	H.OHH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-1,3-dihydro-2,1-benzisothiazole-5-carboxamide 2,2-dioxide N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-	
3206	H N H O F F	hydroxypropyl}-L- norleucinamide  N <sup>1</sup> -((15,2R)-1-(3,5-	
3207	N H H OH H	difluorobenzyl)-3-{[3- (dimethylamino)benzyl] amino}-2- hydroxypropyl)-5-(1,3- oxazol-2-yl)-N³,N³- dipropylisophthalamide	
3208	CI H OH H N F F	2-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-methylisonicotinamide	
3209	OH HOH HOH HOH HOH HOH HOH HOH HOH HOH	N-{(1S,2R)-1-(3,5-difluorobenzy1)-2-hydroxy-3-[(3-iodobenzy1)amino]propy1}-3-{[(2-hydroxyethy1)(propy1)amino]methy1}benzamidedihydrochloride	
3210	F H QH H N F F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-fluoro-4-propoxyphenyl)acetamide	
3211	H QH H N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-methoxy-4-propoxyphenyl)acetamide	

	N OH H	N-{(1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(3- iodobenzyl)amino]propy 1}-3-methyl-5-	
3212	H—CI H—CI	{[methyl(propyl)amino] methyl}benzamide dihydrochloride	
	H QH H H H H H CI	N-{(1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-[(dipropylamino)methyl	
3213	₽ H—CI	]-5-methylbenzamide dihydrochloride	
3214	HO OH H	3- {[butyl(methyl)amino]methyl}-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 2-hydroxy-3-[(3- iodobenzyl)amino]propy 1}-5-methylbenzamide hydrochloride	
3215		N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(piperidin-1-ylsulfonyl)benzamide	
	H N O O O O O O O O O O O O O O O O O O	N-{(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(6-isopropyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl)amino]propyl}-3-methylbenzamide	
3216	F		
3217	P F F N H N N H H OH H	N-((1s,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-4-(3-methoxypropyl)benzamide	
3218	NH <sub>2</sub>	5-amino-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	

	Ţ	$N^{1}$ -[(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-({3-	. [
	L I I I	[(dimethylamino)methyl	. [
	N N N N N N N N N N N N N N N N N N N	benzyl}amino)-2-	
	/ . W H OH H	hydroxypropyl]-5-(1,3-	
	1 1	$oxazol-2-yl)-N^3,N^3-$	
3219		dipropylisophthalamide	
	N N	N-(tert-	T
Į.	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	butoxycarbony1)-3-	
. [	THO H	butyl-N-{(1S,2R)-1-	
j		(3,5-difluorobenzyl)-	
	\ H   H   H   H   H   H   H   H   H	3-[(3-	
		ethylbenzyl)amino]-2-	
	F	hydroxypropyl}-L-	
3220		histidinamide	
	H OH H	N-{(1s,2R)-1-(3,5-	<del> </del>
1		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
1	0 ~ F	hydroxypropyl}-1-	
1		isopentyl-1H-indole-6-	
3221	ľ Y	carboxamide	
3221	<del> </del>		
		N-{(1s,2R)-1-(3,5-	1
1	H OH H	difluorobenzy1)-3-[(3-	
	0=\$	ethylbenzyl)amino]-2-	
	0 0 F	hydroxypropyl}-2-	[ [
ŀ		propyl-2,3-dihydro-	]
		1,2-benzisothiazole-6-	
3222	· ·	carboxamide 1,1-	
5222		dioxide	
İ	\ ~ ^	N-{(1s,2R)-1-(3,5-	. 1
	THE SHEET STATES	difluorobenzy1)-3-[(3-	1
1	0=\$	ethylbenzyl)amino]-2-	
i	) 0 0 F	hydroxypropy1}-2-	
ĺ		ethyl-2,3-dihydro-1,2-	
Í		benzisothiazole-6-	
3223	ļ F	carboxamide 1,1-	
	Br	dioxide	
	ļ <u>I</u>	6-bromo-N-{(1S,2R)-1-	
	н <sub>Он н</sub>	(3,5-difluorobenzyl)-	-
		3-[(3-	
		ethylbenzyl)amino]-2-	
	0 0 F	hydroxypropyl}-2,2-	
		dimethylchromane-8-	
		carboxamide	ļ
3224	<u> </u>		
· <del></del> -	\	N-{(1S,2R)-1-(3,5-	
·		difluorobenzyl)-3-[(3-	ŀ
		ethylbenzyl)amino]-2-	
	, , , , , , , , , , , , , , , , , , , ,	hydroxypropyl}-4-	
		[(methylsulfonyl)methy	
	) Y	l]cyclohexanecarboxami	
3225	l . ⊢	de	
	· —	~~	

		$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-	
		piperidin-4-yl-N³,N³-	
		dipropylisophthalamide	Ì
3226	Ė		
1	l	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-	
	11 1	methyl-5-(1,3-oxazol-	
		2-yl)benzamide	
3227		hydrochloride	
		N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	1 200	ethylbenzyl)amino]-2-	
	/ ``O Ö ₹F	hydroxypropyl}-5-	
		[(methylsulfonyl)methy	
	Ĭ Ť	1]thiophene-2-	ļ
3228	F	carboxamide	
	1	3-	
	A OH	[(cyclohexylamino)meth	
1		y1]-N-{(1S,2R)-1-(3,5-	1
Ĭ		difluorobenzyl)-2-	
		hydroxy-3-[(3-	
		iodobenzyl)amino]propy	
	ļ	1}-5-methylbenzamide	
3229	на	hydrochloride	'
3223		2-(2-chlorophenoxy)-N-	
1	Н Н	{ (1S, 2R) -1-(3,5-	
	N F	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	CI O ///OH	hydroxypropyl}acetamid	
	NH F	e	
	l livit		
1 .			- ,
1			
3230			
2230	l N	N-{(1s,2R)-1-(3,5-	<u> </u>
+	<b> </b>	difluorobenzyl)-3-[(3-	
	N F	ethylbenzyl)amino]-2-	
1		hydroxypropyl}pyrazine	
]	O / "OH \"	-2-carboxamide	
	INFI F		
2221	~ ]		
3231			

Y	O H S A F	N-{(1S,2R)-1-(3,5-	
	S. A. N. A. F	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-	
	OH WOH		
	NH É	(phenylsulfonyl)propan	
	···· ·	amide	
ŀ			
	<b>◇</b> \		
3232	1		
	1	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	N H QH H	ethylbenzyl)amino]-2-	
	$N \sim N \sim N$	hydroxypropyl}-2-	
		1	
Į.		[(2S)-2-	
	6     1	(methoxymethyl)pyrroli	
	1 ~ Y	din-1-y1]-6-	
3233	Ė	methylisonicotinamide	
	H-Cl ,	3-[({(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
			, '
	н би н	ethylbenzyl)amino]-2-	
	HO N N	hydroxypropyl}amino)ca	
		rbonyl]-5-	
		methylbenzoic acid	
		hydrochloride	
2024	Y		
3234	F		
	<b>=</b> N	6-cyano-N-{(1S,2R)-1-	į
		(3,5-difluorobenzyl)-	
	н <sub>Ö</sub> н н	3-[(3-	
	N N N	ethylbenzyl)amino]-2-	
		hydroxypropyl}-2,2-	
	0 0 ~~F '		
		dimethylchromane-8-	
		carboxamide	
3235	ļ <u>ļ</u>		
	HCI	N-{(1S,2R)-1-(3,5-	
	1 1		
	S H OH H	difluorobenzyl)-3-[(3-	
1		ethylbenzyl)amino]-2-	
	N O F	hydroxypropy1}-3-	
	1 · YY	methyl-5-(1,3-thiazol-	
1		2-yl)benzamide	
3236	ļ	hydrochloride	
7233		formic acid compound	
		_	
	I 🗼	with N-{(1S,2R)-1-	*
	H OH H	(3,5-difluorobenzyl)-	
	N N N N N N N N N N N N N N N N N N N	3-[(3-	
		ethylbenzyl)amino]-2-	
1	【	hydroxypropyl}-2-(4-	
	I H OH	ethoxyphenyl)acetamide	
	1 L		
3237	Į F	(1:1)	

		formic acid compound	
		with N-{(1S,2R)-1-	
	l ' l	(3,5-difluorobenzyl)-	
1	Д Н № Н Д	3-[(3-	
			•
		ethylbenzyl)amino]-2-	
	0 0 × F	hydroxypropyl}-3-	
	l' H OH	methy1-5-{[(2S)-2-	
İ	"\forall "	propylpyrrolidin-1-	
	Ö F	yl]carbonyl}benzamide	
3238		(1:1)	
-		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	H PH H	ethylbenzyl)amino]-2-	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	hydroxypropyl}-3-	
	d Ö ≒ √s F	{ [ (2R) -2-(2-	
		methoxyethyl)pyrrolidi	
1		n-1-yl]carbonyl}-5-	
3239	ļ Ė	methylbenzamide	
1	S OH	N-{(1S,2R)-1-(3,5-	
1		difluorobenzyl)-3-[(3-	
1		ethylbenzyl)amino]-2-	
1	Ö 🌠 F	hydroxypropyl}-4-	
		[(methylsulfonyl)methy	
	ľ	1]cyclohexanecarboxami	
3240	Ė	de	
<del>-</del>	,	3-butyl-N-{(1S,2R)-1-	
	N OU		
		(3,5-difluorobenzy1)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-1-	
	<b>Y</b>	methyl-1H-indole-5-	
3241	ļ Ė	carboxamide	
		formic acid compound	
	_	with 2-(1-butyl-2-oxo-	
	н Бн н	1,2-dihydropyridin-4-	
	0		
1		yl)-N-{(1s,2r)-1-(3,5-	
1	H_OH	difluorobenzyl)-3-[(3-	
[	Y	ethylbenzyl)amino]-2-	
		hydroxypropyl}acetamid	
3242		e (1:1)	
	,N-	3-buty1-N-{(1S,2R)-1-	
	[	(3,5-difluorobenzyl)-	
1	HH OH H	3-[(3-	
	H <sub>2</sub> N° H H H	ethylbenzyl)amino]-2-	
	'	hydroxypropyl}-L-	
		histidinamide	
3243	<u> </u>		
2247	F	e e	
1		5-	
1	!	[(diethylamino)methyl]	
	1 1 1		
	0 0 F	$-N^1-\{(1S,2R)-1-(3,5-$	
		-N <sup>1</sup> -{(1S,2R)-1-(3,5-  difluorobenzyl)-3-[(3-	
	N H L N	difluorobenzyl)-3-[(3-	
	N H OH H	difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2-	
	N H OH H	difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N³,N³-	
3244	N H OH H	difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2-	,

	F	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	·
		difluorobenzyl)-3-[(3-	
1		ethylbenzyl)amino]-2-	·
		hydroxypropyl}-5-	
l		[(dimethylamino)methyl	
		$]-N^3,N^3-$	
	, N	dipropylisophthalamide	
3245	<u> </u>	- ((4 - 0-) 2 - (42	
		N-{(1s,2R)-3-[(3-	
	Ń <sub>S</sub> ∕Ò	ethylbenzyl)amino]-1-	
1		[3-(hexyloxy)benzyl]-	
	н ОН Н	2-hydroxypropyl}-3-	
		(1,3-oxazo1-2-	
		yl)benzamide	**570.2
1	Ö	y1/benzamice	
	💚		
3246	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		
		formic acid compound	
		with N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	H OH H	3-[(3-	
	HO N N N N N N N N N N N N N N N N N N N		
		ethylbenzyl)amino]-2-	
	100	hydroxypropyl}-2-(3-	
		hydroxy-4-	
	H~OH	methoxyphenyl)acetamid	ļ ,
3247		e (1:1)	1
		formic acid compound	
-		with N-{(1S,2R)-1-	
[	%//		
	_N_S	(3,5-difluorobenzyl)-	
		3-[(3-	***589.
1		ethylbenzyl)amino]-2-	9
		hydroxypropyl}-4-(1,3-	
	н-соон	thiazolidin-3-	
	ļ	vlsulfonyl) benzamide	
3248		(1:1)	
3440			<del>                                     </del>
		formic acid compound	
		with N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	N'S OH	3-[(3-	
1		ethylbenzyl)amino]-2-	***634.
1		hydroxypropyl}-4-(3,4-	0
1		dihydroisoquinolin-	
1	H-000H	·	-
1	j Ė	2(1H)-	
		ylsulfonyl)benzamide	
3249		(1:1)	
	9,9	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		1) -	***663.
1	Ö <b>→</b>	hydroxypropyl}-4-[(4-	0
		phenylpiperazin-1-	
1	Ţ	yl)sulfonyl]benzamide	1
		1	
3250	'		1

3254				
(3,5-difluorobenzyl) - 3-{(1-(3-ethyl)phemyl) cyclopropyl) amino} - 2-hydroxypropyl) - 1H-benzimidazole-6-carboxamide or ELAN155076   M-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino] - 2-hydroxypropyl) - 5-[(methylsulfonyl)methyl) nincotinamide   M-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl) - 5-(1,3-oxazol-2-yl)-N), N) - (1S,2R) - 1-(3,5-difluorobenzyl) - 3-(3-ethylbenzyl) amino] - 2-hydroxypropyl) - 2-{methyl-5-(4-methylbenzyl) amino] - 2-hydroxypropyl) - 2-{methyl-5-(4-methylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 2-(dipropylamino) - 6-(1,3-oxazol-2-yl) isonicotinamide   M-((1S,2R)-1-(3,5-difluorobenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 3-((3-ethylbenzyl) - 2-hydroxypropyl) - 2-hyd	3251	H OH H	(3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1H-	
difluorobenzyl) -3-[(3-ethylbenzyl)amino] -2-hydroxypropyl) -5-[(methylsulfonyl)methyl]nicotinamide  N-[(1S,2R)-3-(3-[(diethylamino)methyl]benzyl)amino] -1-(3,5-difluorobenzyl) -2-hydroxypropyl] -5-(1,3-oxazol-2-yl)-N³,N³-dipropylisophthalamide  N-((1S,2R)-1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl)amino] -2-hydroxypropyl) -2-[1-methylbenzyl)amino] -2-hydroxypropyl) -2-[1-methylbenzyl)amino] -2-hydroxypropyl) -2-[dipropylamino] -2-hydroxypropyl) -2-(dipropylamino] -2-hydroxypropyl) -2-(dipropylamino] -2-hydroxypropyl) -2-(dipropylamino] -2-hydroxypropyl) -3-[(3-ethylbenzyl)amino] -2-hydroxypropyl) -3-[(3-ethylbenzyl)amino] -2-hydroxypropyl) -3-[(3-ethylbenzyl)amino] -2-hydroxypropyl) -2-methyl-6-(1,3-oxazol-2-yl) isonicotinamide	3253	F F N H H OH H	(3,5-difluorobenzyl)- 3-{[1-(3- ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)-1H- benzimidazole-6- carboxamide or ELAN155076	
N-[(1S,2R)-3-(3-[(diethylamino)methyl]    benzyl)amino]-1-(3,5-    difluorobenzyl)-5-(1,3-    oxazol-2-yl)-N³,N³-    dipropylisophthalamide     N-{(1S,2R)-1-(3,5-    difluorobenzyl)-3-[(3-    ethylbenzyl)amino]-2-    hydroxypropyl)-2-[1-    methyl-5-(4-    methyl-5-(4-    methylbenzoyl)-3-[(3-    ethylbenzyl)amino]-2-    hydroxypropyl)-2-    difluorobenzyl)-3-[(3-    ethylbenzyl)amino]-2-    hydroxypropyl)-2-    (dipropylamino)-6-    (1,3-oxazol-2-    yl)isonicotinamide     N-{(1S,2R)-1-(3,5-    difluorobenzyl)-3-[(3-    ethylbenzyl)amino]-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    methyl-6-(1,3-oxazol-2-    hydroxypropyl)-2-    hydroxypropyl)-2-    hydroxypropyl)-2-    hydroxypropyl)-2-    hydroxypropyl)-2-    hydroxypropyl)-3-[(3-    hydroxypropyl)-3-[(3-    hydroxypropyl)-2-    hydroxypropyl)-3-[(3-    hydroxyprop	3254		<pre>difluorobenzyl) -3-[(3- ethylbenzyl) amino] -2- hydroxypropyl</pre>	**532
N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-[1-methyl-5-(4-methylbenzoy1) -1H-pyrrol-2-yl]acetamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-(dipropylamino) -6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-hydroxypropy1) -2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) amino] -2-hydroxypropy1}-2-methyl-6-(1, 3-oxazol-2-yl) isonicotinamide   N-{(1s, 2r) -1-(3, 5-difluorobenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-[(3-ethylbenzy1) -3-		N H OH H	[(diethylamino)methyl] benzyl)amino)-1-(3,5- difluorobenzyl)-2- hydroxypropyl]-5-(1,3- oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -	,
N-{(1s, 2r) -1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-(dipropylamino)-6-(1,3-oxazol-2-yl) isonicotinamide  N-{(1s, 2r) -1-(3,5-dipropylamino)-6-(1,3-oxazol-2-yl) isonicotinamide  N-{(1s, 2r) -1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-methyl-6-(1,3-oxazol-2-yl) isonicotinamide		THE PERSON OF TH	difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-2-[1- methyl-5-(4- methylbenzoyl)-1H-	
N-{(1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-6-(1,3-oxazol-2-yl)isonicotinamide		F F N N N N N N N N N N N N N N N N N N	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-(1,3-oxazol-2-	
3258 , N O		F F N N N N N N N N N N N N N N N N N N	<pre>difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- methyl-6-(1,3-oxazol-</pre>	

<del></del>			
1	Ę	1-buty1-N-((1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	L\F	3-{[1-(3-	
	^ / ~	ethynylphenyl)cyclopro	
		pyl]amino}-2-	1
		F - "	
		hydroxypropyl)-1H-	
	: <b>/</b>	benzimidazole-5-	
3259		carboxamide	
	\ \	N-{(1S,2R)-1-(3,5-	
i		difluorobenzyl)-2-	
		hydroxy-3-[(6-	
		isopropy1-2,2-dioxido-	
	l II • <b>=</b>		
	1 () , >=/	3,4-dihydro-1H-	
	·	isothiochromen-4-	
	l <b>––</b> (, ,)	yl)amino]propyl}-3-	
		methylbenzamide	
3260	F	_	
	NH NH	$N^{1}-\{(1S,2R)-1-(3,5-$	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	1 / )		
		hydroxypropyl}-5-	**649.6
	0	piperidin-3-yl-N³,N³-	. ]
		dipropylisophthalamide	l i
		hydrochloride	
3261	<u> </u>		
		3-	
		{ [benzyl (methyl) amino]	
	н <sub>бн</sub> н 📗	$methyl}-N-{(1S,2R)-1-}$	}
		(3,5-difluorobenzyl)-	
1		2-hydroxy-3-[(3-	**684.2
l		iodobenzyl)amino]propy	
		1}-5-methylbenzamide	
20.50	j + ''- ''		
3262		dihydrochloride	
		formic acid compound	
		with N-{(1S,2R)-1-	
	0, 0	(3,5-difluorobenzyl)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	
-		hydroxypropyl}-4-{[4-	<u> **</u> *680.
	•	(4-	9
	H-C00H		
	 	fluorophenyl)piperazin	
1	H-COO!	<b>-1-</b>	
Ì		yl]sulfonyl}benzamide	
3263		(2:1)	
	9, 9	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	Man H BH H L J	ethylbenzyl)amino]-2-	ĺ
			****572
1		hydroxypropyl}-4-	""5/2
1		(pyrrolidin-1-	· .
L	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	ylsulfonyl)benzamide	1
3264	ļk		<u></u>

		<u> </u>	
		formic acid compound	
	<b>%</b> , <i>p</i>	with N-{(1S,2R)-1-	
	~,,,'S	(3,5-difluorobenzyl)-	1
		3-[(3-	****
		ethylbenzyl)amino]-2-	
	Ö 🍾 F	hydroxypropyl}-4-	572.0
	H-COOH	(pyrrolidin-1-	
	Į "······	ylsulfonyl)benzamide	
	<b>-</b>		
3265		(1:1)	
i	_	formic acid compound	·
		with N-{(1S,2R)-1-	1
İ	ور ہ	(3,5-difluorobenzyl)-	
1		3-[(3-	
İ		ethylbenzyl)amino]-2-	****
		hydroxypropyl}-4-({4-	
		[3-	731.0
1	CF9 H-COOH	(trifluoromethyl)pheny	
	F H-COOH	l]piperazin-1-	
1		y1}sulfonyl)benzamide	
2266		(2:1)	
3266	100	<u> </u>	
		N-{(1s,2R)-1-(3,5-	
	N,S OH	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	\ \lambda \lambda \lambda \lambda \\ \lambda \lambda \lambda \\ \lambda \lambda \\ \lambda \lambda \\ \lambda \lambda \\	hydroxypropyl}-4-	****546
	0 Y	[(dimethylamino)sulfon	
		yl]benzamide	
3267	Ļ		
		formic acid compound	•
1		with N-{(1S, 2R)-1-	
	N S OH	(3,5-difluorobenzyl)-	
		3-[(3-	****
	l A J A A A A	ethylbenzyl)amino]-2-	546.0
	l V	hydroxypropyl}-4-	340.0
	нсоон	,	,
	l F	[(dimethylamino)sulfon	
3268		yl]benzamide (1:1)	
	9.00	N-{(1S,2R)-3-[(3-	
	-SN-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N-N	ethylbenzyl)amino]-1-	
	H N N	[3-(hexyloxy)benzyl]-	
		2-hydroxypropy1}-2-	**587.5
		[(methylsulfonyl)amino	
	Y	]-1,3-oxazole-4-	
3269	\\o	carboxamide	
	OU OU	N-{(1S,2R)-1-(3,5-	<del></del>
	D S O H OH H	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-6-	**532
	- Y Y .	1	ł
		[(methylsulfonyl)methy	
3270	ļ	1]nicotinamide	
		1-buty1-N-{(1S,2R)-1-	<del></del>
	H OH H	(3,5-difluorobenzyl)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	**498.4
			4,70.4
		hydroxypropyl}-5-	1
	I' I	methyl-1H-pyrrole-2-	
3272	<u>F</u>	carboxamide	L
			,

3273	H QH H N N N H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-pyrrol-2-ylmethyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamideN <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-piperazin-1-yl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamidehydrochloride	**541.2 **650.4
3276	H H H H H H H H H H H H H H H H H H H	N <sup>2</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-6- methyl-N <sup>4</sup> ,N <sup>4</sup> - dipropylpyridine-2,4- dicarboxamide N <sup>2</sup> -(tert- butoxycarbonyl)-N <sup>1</sup> - {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-D- norleucinamide	
		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-D-norleucinamide  formic acid compound with 4-{[(4-chlorophenyl)(methyl)amino]sulfonyl}-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-difluorobenzy	*** 642.0
3281	н-ооои	ethylbenzyl)amino]-2- hydroxypropyl}benzamid e (1:1)	-

3282	ON OH HOOSE	formic acid compound with 4- {[benzyl(phenyl)amino] sulfonyl}-N-{(1S,2R)- 1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}benzamid e (1:1)	*** 684.1
3283	ON OH HOOOH	formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4- (morpholin-4- ylsulfonyl)benzamide (1:1)	***588. 1
3285	O O O F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxo-4-propylcyclohexyl)acetamide	**515.4
3286		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(3-oxocyclohexyl)acetamide	**473.3
3287	N N N N N N N N N N N N N N N N N N N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,1-dipropyl-3,4-dihydro-1H-isochromene-7-carboxamide	**579.4
3288	N=\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	formic acid compound with 4-{[(2-cyanoethyl)(methyl)amino]sulfonyl}-N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}benzamide (1:1)	***585. 0

	o o formic acid co	mpound	
	NS H OH H [[cyclohexyl(m	ethvllam	
	ino]sulfonyl}-		
	$\{(1S, 2R) - 1 - (3, 2R) - 1 - (3, 2R) - 1 - (3, 2R) - 1 - (3, 2R) - (3, 2R$		***614.
	difluorobenzyl		0
	H-000H ethylbenzyl) an		
	F hydroxypropyl)		
3289	e (1:1)	Denzania	
5209	formic acid co	- Equa	
	with N-{(1S, 2F		
	N S H OH H (3,5-difluorok		
	3-[(3-	Jenzyr) -	
	o F ethylbenzyl) an	nino1-2-	***637.
	hydroxypropyl)		0
	+cook { [methyl (2-pyr	1412	
	[{[methy1(2-pyr   +com ylethy1)amino]	gul fonzi	
3290	}benzamide (2:	- 1	
3430	penzamide (2:		
	with N-{(1S, 2F	- 1	
		-	
	N QH H (3,5-difluorok) 3-[(3-	_	
1	ethylbenzyl) an	.:	***608.
		-	1
	hydroxypropyl)  H-XXXIII [methyl (pheny		
3291	sulfonyl)benza	mirae	
3491	formic acid co		<del></del>
	with 4-	nifomia	•
	QH   ([benzyl(meth)	allaminol	
	sulfonyl)-N-{		
	1-(3,5-	(15,2K)-	***622.
	difluorobenzyl	11-3-1(3-	1
1	ethylbenzyl) an		
	hydroxypropyl)		
3292	e (1:1)	Delizamita	
5252	formic acid co	mnound	
1	with N-{(15,2)		
	N S H OH H (15,21	-	
	3-[(3-	_	
	ethylbenzyl) an	ninol-2-	***636.
	hydroxypropyl)	- 1	1
	How [[methyl(2-	·	
1	phenylethyl) an	ninoleulf	
3293	onyl}benzamide		
	onylybenzamica		
	with 4-		
	N S H OH H ([ally] (methy)	l)aminole	
	ulfonyl}-N-{(1	10 00 1 1	
	(3,5-difluoro		***572.
	3-[(3-	~~y ± / =	1
	+coordethylbenzyl) ar	nino1-2-	
i	hydroxypropyl)		
3294	e (1:1)	, werreamed	
243±	[G (T:T)		

	0, 0	formic acid compound	
		with 4-{[[2-	
1	N J H OH H	(diethylamino)ethyl](m	
		ethyl)amino]sulfonyl}-	***631.
1	N. Ö ***	N-{(1S,2R)-1-(3,5-	_
1		difluorobenzyl)-3-[(3-	1.
	H-COOH	ethylbenzyl)amino]-2-	
	F H-cooн	hydroxypropyl}benzamid	
2205		e (2:1)	
3295		formic acid compound	
	Q, p		
<u> </u>	S au	with N-{(1S,2R)-1-	
1		(3,5-difluorobenzyl)-	
		3-[(3-	***574.
Ì	Ö 🍑 F	ethylbenzyl)amino]-2-	1
•		hydroxypropyl}-4-	_
-	H-COOH	{[methyl(propyl)amino]	
	F F	sulfonyl}benzamide	
3296		(1:1)	
		formic acid compound	
	0.0	with 4-	
		{ [butyl (methyl) amino]s	
	N/S/N H OH H	ulfony1}-N-{(1S,2R)-1-	
			***588.
		(3,5-difluorobenzyl)-	1
		3-[(3-	·
1	н-соон	ethylbenzyl)amino]-2-	·
	F F	hydroxypropyl}benzamid	
3297		e (1:1)	
	0 0	formic acid compound	
1		with N-{(1s,2R)-1-	
	H OH H	(3,5-difluorobenzyl)-	
		3-[(3-	***602.
		ethylbenzyl)amino]-2-	
		hydroxypropy1}-4-	1
•	H-coop	{ [methyl (pentyl) amino]	
	F	sulfonyl}benzamide	
3298	•	(1:1)	
	,	formic acid compound	
1		with N-{(1s, 2R)-1-	
		(3,5-difluorobenzyl)-	· •
	N'S H OH H	3-[(3-	'
-			***602.
	│ <del>│</del>	ethylbenzyl)amino]-2-	1
	r` []	hydroxypropyl}-4-	"
	н-соон	{[isopentyl(methyl)ami	
i .	, <u></u>		
	Ė	no]sulfonyl}benzamide	
3299	Ė	(1:1)	
3299	Ė	-	· ·
3299	Ė AU	(1:1)	· .
3299	F OH H OH H OH H	(1:1) 2-butyl-N-{(1S,2R)-1-	
3299	F OH H	(1:1) 2-butyl-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3-	
3299	N N N N N N N N N N N N N N N N N N N	(1:1) 2-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-	**550.3
3299	N N N H-CI	(1:1) 2-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-	**550.3
3299	N N N N N N N N N N N N N N N N N N N	(1:1)  2-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-  1,2,3,4-	**550.3
3299	N N N H-CI	(1:1)  2-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-  1,2,3,4-tetrahydroisoquinoline	**550.3
3299	N N N H-CI	(1:1)  2-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-  1,2,3,4-	**550.3

	formic acid compound  Q, Q with N-{(1S,2R)-1-	
	WICH N={(15,2R)-1-	
1	(3,5-difluorobenzyl)-	
	3-[(3-	1
	ethylbenzyl)amino]-2-	***615.
ľ	hydroxypropyl}-4-	0
	H-COOH [{ [methyl (1-	ľ
	methylpyrrolidin-3-	
2201	HOOOH yl)amino]sulfonyl}benz	
3301	amide (2:1)	
	$\mathbb{N}^{1}$ -((1s,2R)-1-(3,5-	
	difluorobenzyl)-3-{[1-	l
i	(4-ethylpyridin-2-	
1	l l company l company l l company l l company l l company l l company l l company l company l company l l company	
	N 2-hydroxypropyl)-5-	
1		
	$H \stackrel{\text{N}}{\text{OH}} \stackrel{\text{H}}{\text{H}} = (1,3-\text{oxazol}-2-\text{yl}) - (1,3-ox$	
j	dipropylisophthalamide	
1	N 0	
2202		
3302		
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3303		1
	N-((1s,2R)-1-(3,5-	
ŀ	difluorobenzyl)-3-{[1-	
}	(3-	i
	ethynylphenyl)cyclopro	
	pyl]amino}-2-	
		1
3304	hydroxypropyl)-3-(2-	}
5304	methoxyethyl)benzamide	
1	1-butyl-N-((1S,2R)-1-	
1	[(3,5-difluorobenzyl)-	1
	3-{[1-(3-	.
-	ethynylphenyl)cyclopro	.
	pyllamino}-2-	
	hydroxypropyl)-2-(2-	
1	methoxyethyl)-1H-	
	benzimidazole-6-	
3305	carboxamide	
	O OH s L-alpha-glutamyl-L-	
[	Valy1-N1-{(1S,2R)-1-	
1	HN N N N (3,5-dilluorobenzyl) -	
I		1
1	ethylbenzyl)amino]-2-	. [
3306	hydroxypropyl}-L-	
5300	f methioninamide	
		———

([cyclohexyl (methyl) am ino] methyl) -N- ((15, 2R) -1 - (3, 5- difluorobenzyl) amino] propy 1) -5-methylbenzamide hydrochloride formic acid compound with N- (15, 2R) -1 - (3, 5- difluorobenzyl) amino] -2- hydroxyropyl) acetamid e (1:1)    3-bicyclo[2.2.1]hept-2-2-yl-N-(15, 2R) -1 - (3, 5- difluorobenzyl) -3-[(3- ethylbenzyl) amino] -2- hydroxypropyl) benzamid e (1:1)   3-bicyclo[2.2.1]hept-2-yl-N-(15, 2R) -1 - (3, 5- difluorobenzyl) -3-[(3- ethylbenzyl) amino] -2- hydroxypropyl) benzamid e (1:1)   3-bicyclo[2.2.1]hept-2-yl-N-(15, 2R) -1 - (3, 5- difluorobenzyl) -3-[(1- (3, 5- difluorobenzyl) -3-[(1- (3, 5- difluorobenzyl) -3-[(1- (3, 2R) -1 - (3, 5- difluorobenzyl) -2- hydroxypropyl) -4-(2- methoxyethyl) benzamide   (1:3- oxazol-2- yl) isonicotinamide   (1:3- oxazol-2- yl) isonicotinamide   (1:3- oxazol-2- hydroxypropyl) -2- hydroxypropyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzamide   (3, 5- difluorobenzyl) -3- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydroxypropyl) -4- methylbenzyl) amino] -2- hydrox			· · · · · · · · · · · · · · · · · · ·	
Inco methyl)-N- ((15, 2R)-1-(3, 5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl) amino]propy   1)-5-methylbenzamide hydrochloride   formic acid compound with 2-(4-butyl-2,5-difluorobenzyl)-3-[(3-iodobenzyl) amino]-2-hydroxypropyl) acetamid   e (1:1)		1	3-	
(1(s, 2R)-1-(3, 5-diffluorobenzy1)-2-hydroxy-3-(3-iodobenzy1) amino]propy   1)-5-methylbenzamide hydrochloride   formic acid compound with 2-(4-buty1-2,5-dioxopiperazin-1-y1)-N-(1(s, 2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1) acetamide   (1:1)   3-bicyclo[2.2.1]hept-2-y1-N-(1(s, 2R)-1-(3,5-difluorobenzy1)-3-([1-(3,5-difluorobenzy1)-3-([1-(3,5-difluorobenzy1)-3([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-3-([1-(3,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropy1)-2-hydroxypropy1)-2-hydroxypropy1)-3-methylbenzamide   formic acid compound with N-((1(s,2R)-1-(3,5-difluorobenzy1)-3-([1s)-1,2,3,4-difluorobenzy1)-3-methylbenzamide   formic acid compound with N-((1(s,2R)-1-(3,5-difluorobenzy1)-3-methylbenzamide   formic acid compound with N-((1(s,2R)-1-(3,5-difluorobenzy1)-3-([1s)-1,2]-methylbenzamide   formic acid compound with N-((1(s,2R)-1-(s,5-difluorobenzy1)-3-([1s)-1,2]-methylbenzamide   formic acid compound with N-((1				· ·
difluorobenzyl) -2- hydroxy-3-[(3-iodobenzyl) amino]propy   1)-5-methylbenzamide hydrochloride   formic acid compound with 2-(4-butyl-2,5-dioxopiperazin-1-yl)-N-(1(1,2,2R)-1-(3,5-difluorobenzyl))-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) acetamid   e (1:1)   3-bicyclo[(2:2.1])hept-2-yl-N-((15,2R)-1-(3,5-difluorobenzyl))-3-[(1-(3,5-difluorobenzyl))-3-[(1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1-(3,2R)-1-(3,5-difluorobenzyl))-3-([1,3-oxazol-2-yl)] isonicotinamide   N-((15,2R)-1-(3,5-difluorobenzyl))-3-([1,3-oxazol-2-yl)] isonicotinamide   N-((15,2R)-1-(3,5-difluorobenzyl))-3-([1,3-oxazol-2-yl)] isonicotinamide   N-((15,2R)-1-(3,5-difluorobenzyl))-3-([1,3-oxazol-2-yl)] isonicotinamide   N-((15,2R)-1-(3,5-difluorobenzyl))-3-([1,3-oxazol-2-yl)] isonicotinamide   N-((15,2R)-1-(3,5-difluorobenzyl))-3-([1,3-difluoroben				
hydroxy-3-[(3-iodobenzyl) amino]propy   1)-5-methylbenzamide   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrochloride   hydrocypropyl]-3-[(3-ethylbenzyl)]   hydroxypropyl]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(3-ethylbenzyl)]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-ethylbenzyl)]]   -3-[(1-(3-(3-ethylbenzyl)]]]   -3-[(1-(3-(3-(3-ethylbenzyl)]]]   -3-[(1-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-(3-				
iodobenzyl) amino] propy   1)-5-methylbenzamide   hydrochloride   formic acid compound   with 2-(4-butyl-2,5-dioxopiperazin-1-yl) - N-(1(1,8,2R)-1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl) acetamid   e (1:1)   3-bicyclo[(2,2,1]) hept-2-yl-N-((1,8,2R)-1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl) benzamid   e (1:1)   (3-ethylbenzyl) amino] -2-hydroxypropyl) -4-(2-methoxyethyl) benzamide   (3-ethynylphenyl) cyclopro pyl] amino) -2-hydroxypropyl) -4-(2-methoxyethyl) benzamide   (3-ethynylphenyl) cyclopro pyl] amino) -2-hydroxypropyl) -3-[(1-(3-ethynylphenyl) cyclopro pyl] amino) -2-hydroxypropyl) -2-(dipropylamino) -6-(1,3-oxazol-2-hydroxypropyl) -2-(dipropylamino) -6-(1,3-oxazol-2-hydroxypropyl) -2-(dipropylamino) -6-(1,3-oxazol-2-hydroxypropyl) -3-methylbenzamide   formic acid compound   mith N-((1,8,2R)-1-(3,5-difluorobenzyl) -3-methylbenzamide   formic acid compound   mith N-((1,8,2R)-1-(3,5-difluorobenzyl) -3-(1,8)-(3,5-difluorobenzyl) -3-(3,5-difluorobenzyl)		0 \_F		<b> </b> **676.2
3307    No.   1)-5-methylbenzamide hydrochloride formic acid compound with 2-(4-butyl-2,5-dioxopiperazin-1-yl)-N-((15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamid   (1:1)   3-bicyclo[2,2,1]hept-2-yl-N-((15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamid   (1:1)   3-bicyclo[2,2,1]hept-2-yl-N-((15,2R)-1-(3,5-difluorobenzyl)-3-[(1-(3,5-difluorobenzyl)-3-[(1-(3,5-difluorobenzyl)-3-(1-(3-ethynylphenyl)cyclopro pyl]amino)-2-hydroxypropyl)-4-(2-methoxyethyl)benzamide   (1:3,2R)-1-(3,5-difluorobenzyl)-3-([1-(3,3-difluorobenzyl)-3-([1-(3,3-difluorobenzyl)-3-([1-(3,3-difluorobenzyl)-3-([1-(3,3-difluorobenzyl)-3-([1-(3,3-difluorobenzyl)-2-hydroxy-3-([15)-1,2,3,4-tetrahydromaphthalen-1-ylamino]propyl)-3-methylbenzamide   (3,5-difluorobenzyl)-3-([3,5-difluorobenzy			hydroxy-3-[(3-	
hydrochloride   formic acid compound   with 2-(4-butyl-2,5-dioxopiperazin-1-yl) - N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-ethylbenzyl)amino]-2-hydroxypropyl)acetamid   e (1:1)   3-bicyclo[2.2.1]hept-2-yl-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([3-ethylbenzyl)amino]-2-hydroxypropyl)benzamid   e (1:2)   s-difluorobenzyl)   s-(13,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-4-(2-methoxyethyl)benzamide   N-((1S,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl)cyclopropyl]amino)-2-hydroxypropyl)-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide   N-((1S,2R)-1-(3,5-difluorobenzyl)-3-methylbenzamide   N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-([1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]propyl}-3-methylbenzamide   N-((1S,2R)-1-(3,5-difluorobenzyl)-3-methylbenzamide		l E	<pre>iodobenzyl)amino]propy</pre>	İ
3310  hydrochloride formic acid compound with 2-(4-buty1-2,5- dioxopiperazin-1-y1)- N-((1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1)benzamid e (1:1)  3-bicyclo[2.2.1]hept- 2-y1-N-((1S,2R)-1- (3,5-difluorobenzy1)- 3-[(3- ethylbenzy1)amino]-2- hydroxypropy1)benzamid e  3311  F  A  A  B  B  B  B  B  B  B  B  B  B  B		HCI		ļ
# OH H With 2-(4-buty1-2,5-dioxopiperazin-1-y1) - N-(1(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) amino]-2-hydroxypropyl) benzamid e(1:1)  3-bicyclo[2.2.1]hept-2-y1-N-((1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) benzamid ethylbenzyl) benzamid ethylbenzyl) benzamid ethylbenzyl) cyclopropyl) amino]-2-hydroxypropyl)-3-[[1-(3-ethynylphenyl) cyclopropyl) amino]-2-hydroxypropyl)-4-(2-methoxyethyl) benzamide N-((1s,2R)-1-(3,5-difluorobenzyl)-3-([1-(3-ethynylphenyl) cyclopropyl) amino]-2-hydroxypropyl)-2-(dipropylamino)-2-hydroxypropyl)-2-(dipropylamino)-6-(1,3-oxazo1-2-yl) isonicotinamide N-((1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1s)-1,2,3,4-tetrahydronaphthalen-1-ylamino]propyl)-3-methylbenzamide formic acid compound with N-((1s,2R)-1-(3,5-difluorobenzyl)-3-methylbenzamide formic acid compound with N-((1s,2R)-1-(3,5-difluorobenzyl)-3-methylbenzamide ethylbenzyl) amino]-2-hydroxypropyl}-4-	3307		hydrochloride	
dioxopiperazin-1-yl) - N-((1s, 2R) -1 - (3, 5-difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl} acetamid e (1:1)   3-bicyclo[2.2.1]hept-2-yl-N-((1s, 2R) -1-(3, 5-difluorobenzyl) - 3-[(3-ethylbenzyl) amino] -2-hydroxypropyl} benzamid e   3-(butylamino) -N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-[(1-(3-ethylpenyl) cyclopropyl]amino] -2-hydroxypropyl) -4-(2-methoxyethyl) benzamid e   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-([1-(3-ethynylphenyl) cyclopropyl]amino] -2-hydroxypropyl) -4-(2-hydroxypropyl) -2-(dipropylamino) -6-(1, 3-oxazol-2-yl) isonicotinamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -2-hydroxy-3-[(1s) -1, 2, 3, 4-etrahydronaphthalen-1-ylamino] propyl -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide   N-((1s, 2R) -1-(3, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl) -3-((1s, 5-difluorobenzyl	!	•	formic acid compound	
3310    The property of the pr		H <sup>QH</sup> H [ ]	·	
3310    H OH   difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl) acetamid   e (1:1)   3-bicyclo[2.2.1]hept-2-yl-N-(1(s,2R)-1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl) benzamid   e (1:1)   3-((3-ethynlphenyl) cyclopro   pyl]amino) -2-hydroxypropyl) -4-(2-hydroxypropyl) -4-(2-hydroxypropyl) -4-(2-hydroxypropyl) -3-[(1-(3-ethynlphenyl) cyclopro   pyl]amino) -2-hydroxypropyl) -2-(dipropylamino) -6-(1,3-oxazol-2-yl) isonicotinamide   N-((1s,2R)-1-(3,5-difluorobenzyl) -2-hydroxypropyl) -2-hydroxypropyl) -2-hydroxypropyl) -2-hydroxypropyl) -2-hydroxypropyl) -3-methylbenzamide   formic acid compound   with N-(1s,2R)-1-(3,5-difluorobenzyl) -3-methylbenzamide   formic acid compound   with N-(1s,2R)-1-(3,5-difluorobenzyl) -3-(1s,5-difluorobenzyl)				
## Open control of the property of the propert		N O F		
hydroxypropyl)acetamid e (1:1) 3-bicyclo(2.2.1]hept- 2-yl-N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3-ethylbenzyl)amino]-2- hydroxypropyl)benzamid e (1:3,5-difluorobenzyl)-3-{[1- (3,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3-ethynlphenyl)cyclopro pyl]amino]-2- hydroxypropyl)-4-(2- methoxyethyl)benzamide N-((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3-ethynlphenyl)cyclopro pyl]amino]-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide N-{(1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl)-3- methylbenzamide formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3-ethylbenzyl)amino]-2- hydroxypropyl)-4-  ***602. 0		H_OH		
3-bicyclo[2.2.1]hept- 2-yl-N-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3-ethylbenzyl)amino]-2- hydroxypropyl)benzamid e  3-(butylamino)-N- ((1s,2R)-1-(3,5- difluorobenzyl)-3-([1- (3-ethynylphenyl)cyclopro pyl]amino]-2- hydroxypropyl)-4-(2- methoxyethyl)benzamide N-((1s,2R)-1-(3,5- difluorobenzyl)-3-([1- (3-ethynylphenyl)cyclopro pyl]amino]-2- hydroxypropyl)-2- (dipropylamino]-6- (1,3-oxazol-2- yl)isonicotinamide N-((1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-((1s,2R)-1- (3,5-difluorobenzyl)- 3-((3-ethylbenzyl)amino]-2- hydroxypropyl)-4-  ***602.0  ***602.0  ***602.0  ***603.0  *		Ţ	ethylbenzyl)amino]-2-	ļ
3-bicyclo[2.2.1]hept- 2-yl-N-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)benzamid e  3-(butylamino)-N- ((1s,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3,2R)-1-(3,5-difluorobenzyl)-2-hydroxypropyl)-2-(dipropylamino)-6-([1,3-oxazol-2-yl)isonicotinamide N-((1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1s)-1,2,3,4-tetrahydroaphthalen-1-ylamino]propyl)-3-methylbenzamide  13313    H   OH		· '		
2-y1-N-{(1s, 2R) -1- (3,5-difluorobenzyl) - 3-[(3-ethylbenzyl) amino] -2-hydroxypropyl) benzamid e 3-(butylamino) -N- ((1s, 2R) -1- (3, 5-difluorobenzyl) -3-{[1-(3-ethynylphenyl) cyclopropyl] amino} -2-hydroxypropyl) -4-(2-methoxyethyl) benzamide N-((1s, 2R) -1- (3, 5-difluorobenzyl) -3-{[1-(3-ethynylphenyl) cyclopropyl] amino} -2-hydroxypropyl) -2-(dipropylamino) -6-(1, 3-oxazol -2-yl) isonicotinamide N-((1s, 2R) -1- (3, 5-difluorobenzyl) -2-hydroxy-3-[(1s) -1, 2, 3, 4-tetrahydronaphthalen-1-ylamino] propyl} -3-methylbenzamide formic acid compound with N-{(1s, 2R) -1-(3, 5-difluorobenzyl) -3-methylbenzamide formic acid compound with N-{(1s, 2R) -1-(3, 5-difluorobenzyl) -3-(3-ethylbenzyl) amino] -2-eth	3809			
3310    (3,5-difluorobenzyl) - 3-[(3-ethylbenzyl) amino] - 2-hydroxypropyl) benzamid   (15,2R) - 1-(3,5-difluorobenzyl) - 3-([1-(3-ethynylphenyl) cyclopropyl) amino) - 2-hydroxypropyl) - 4-(2-methoxyethyl) benzamide   (15,2R) - 1-(3,5-difluorobenzyl) - 3-([1-(3-ethynylphenyl) cyclopropyl) amino) - 2-hydroxypropyl) - 2-(dipropylamino) - 6-(1,3-oxazol - 2-yl) isonicotinamide   (15,2R) - 1-(3,5-difluorobenzyl) - 2-hydroxy-3-[(1S) - 1,2,3,4-tetrahydronaphthalen-1-ylamino] propyl} - 3-methylbenzamide   (3,5-difluorobenzyl) - 3-(3,5-difluorobenzyl)		F	1	
3-[(3-ethylbenzyl) amino]-2-hydroxypropyl) benzamid elements of the property o		<u> </u>		
ethylbenzyl) amino] -2- hydroxypropyl) benzamid e  3-(butylamino) -N- ((1s, 2R) -1-(3, 5- difluorobenzyl) -3-{[1- (3- ethynylphenyl) cyclopro pyl] amino} -2- hydroxypropyl) -4-(2- methoxyethyl) benzamide N-((1s, 2R) -1-(3, 5- difluorobenzyl) -3-{[1- (3- ethynylphenyl) cyclopro pyl] amino} -2- hydroxypropyl) -2- (dipropylamino) -6- (1, 3-oxazol-2- yl) isonicotinamide N-((1s, 2R) -1-(3, 5- difluorobenzyl) -2- hydroxy-3-[(1s) - 1, 2, 3, 4- tetrahydronaphthalen- 1-ylamino] propyl} -3- methylbenzamide  formic acid compound with N-((1s, 2R) -1- (3, 5-difluorobenzyl) - 3-[(3- ethylbenzyl) amino] -2- hydroxypropyl} -4-  ***602.		L L F	-	
assistance of the property of		A GH	* *	
3310    Comparison of the comp		N N N N N N N N N N N N N N N N N N N	1	
3310    County lamino) -N-		H H OH H	hydroxypropyl}benzamid	
((15, 2R) -1-(3, 5- difluorobenzyl) -3-{[1- (3- ethynylphenyl) cyclopro pyl]amino} -2- hydroxypropyl) -4-(2- methoxyethyl) benzamide N-((15, 2R) -1-(3, 5- difluorobenzyl) -3-{[1- (3- ethynylphenyl) cyclopro pyl]amino} -2- hydroxypropyl) -2- (dipropylamino) -6- (1, 3-oxazol-2- yl) isonicotinamide N-{(15, 2R) -1-(3, 5- difluorobenzyl) -2- hydroxypropyl) -2- hydroxy-3-[(15) - 1, 2, 3, 4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(15, 2R) -1- (3, 5-difluorobenzyl) - hydroxy-3-[(15) - 1, 2, 3, 4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(15, 2R) -1- (3, 5-difluorobenzyl) - 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-4-	3310		<u>e</u>	
difluorobenzyl) -3-{[1- (3- ethynylphenyl) cyclopro pyl]amino}-2- hydroxypropyl) -4-(2- methoxyethyl) benzamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl) cyclopro pyl]amino}-2- hydroxypropyl) -2- (dipropylamino)-6- (1,3-oxazol-2- yl) isonicotinamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3313  formic acid compound with N-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-4-		Ę		,
Comparison of the comparison	]			
ethynylphenyl) cyclopro pyl]amino}-2- hydroxypropyl)-4-(2- methoxyethyl) benzamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl) cyclopro pyl]amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl) isonicotinamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-		ı, o		
pyl]amino}-2- hydroxypropyl)-4-(2- methoxyethyl)benzamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-			] · -	
hydroxypropyl) -4-(2-				
methoxyethyl) benzamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl) cyclopro pyl] amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazo1-2- yl) isonicotinamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino] propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-4-	1	~~ ·	F -	
N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2-(dipropylamino)-6-(1,3-oxazol-2-yl)isonicotinamide  N-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]propyl}-3-methylbenzamide  formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-methylbenzamide  formic acid compound with N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-    3314				
difluorobenzyl) -3-{[1-(3-ethynylphenyl) cyclopropyl] amino} -2-hydroxypropyl) -2-(dipropylamino) -6-(1,3-oxazol-2-yl) isonicotinamide  N-{(1s,2r)-1-(3,5-difluorobenzyl) -2-hydroxy-3-[(1s)-1,2,3,4-tetrahydronaphthalen-1-ylamino] propyl} -3-methylbenzamide  formic acid compound with N-{(1s,2r)-1-(3,5-difluorobenzyl) -3-methylbenzamide}  formic acid compound with N-{(1s,2r)-1-(3,5-difluorobenzyl) -3-[(3-ethylbenzyl) amino] -2-hydroxypropyl} -4-	3311			
(3-ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2r)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-				
ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2r)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-  ***602.		, F		
pyl]amino}-2- hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1S)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-  ***602.	1		•	
hydroxypropyl)-2- (dipropylamino)-6- (1,3-oxazol-2- yl)isonicotinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2r)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-				
(dipropylamino) -6- (1,3-oxazol-2- yl) isonicotinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2r)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-	]		· •	
(1,3-oxazo1-2- yl)isonicotinamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(1s)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-		N H H OHH		
yl) isonicotinamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino] propyl}-3-methylbenzamide  formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-ethylbenzyl) a		1		
## OH H H diffuorobenzyl)-2- hydroxy-3-[(1S)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-	3313	N~ `O		
difluorobenzyl) -2- hydroxy-3-[(1S)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino] propyl}-3- methylbenzamide  formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-4-	2314			
hydroxy-3-[(1S)- 1,2,3,4- tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-				
formic acid compound with N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-				
tetrahydronaphthalen- 1-ylamino]propyl}-3- methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-				
formic acid compound with N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-				
methylbenzamide  formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- http://documpound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 0  ***602.				
formic acid compound with N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- howethydroxypropyl}-4-				
formic acid compound with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- howethydroxypropyl}-4-	3313		me cult to eur samt de	,
with N-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-		0, 0	formic acid compound	
(3,5-difluorobenzyl) - ***602. 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-		XV/	_	
3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-4-	]			
ethylbenzyl)amino]-2-  *****hydroxypropyl}-4-				
hydroxypropyl}-4-				0
	3314		(dipropylamino) sulfon	

<del></del>		I	
	·•	[(dipropylamino)sulfon	
		yl]benzamide (1:1) formic acid compound	
	Q, p	with 4-	:
		[(diethylamino)sulfony	
		$[1]-N-\{(1S,2R)-1-(3,5-$	***574.
1		difluorobenzyl)-3-[(3-	0
		ethylbenzyl)amino]-2-	"
	н-соси	hydroxypropyl}benzamid	
3315	Ė	e (1:1)	
3313	1	4-butyl-N-{(1S,2R)-1-	
	o=\$=0	(3,5-difluorobenzyl)-	
	N Ou	3-[(3-	
		ethylbenzyl)amino]-2-	
	j ju vy	hydroxypropyl}-1-	
		(methylsulfonyl)-	**629
		1,2,3,4-	[
		tetrahydroquinoxaline-	
	<b> </b>	6-carboxamide	1
3316			<u></u>
	H OH H	1-butyl-N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
		3-[(3-	**546.3
j		ethylbenzyl)amino]-2-	3 = 0.3
1		hydroxypropyl}isoquino	
3317	F F	line-7-carboxamide	
		5-	
	\_ /	[[butyl(methyl)amino]m	
İ	L L PH H PH H PH	ethyl}-N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)- 3-[(3-	**544.3
	0 1	ethylbenzyl)amino]-2-	7.7544.3
	l ⊬ н—α	hydroxypropyl}thiophen	
	<sup>‡</sup> н—а	e-2-carboxamide	
3318		dihydrochloride	
		3-	
		[[butyl(methyl)amino]m	
•	J. Charles	ethyl}-N-((1S,2R)-1-	•
	H OH H	(3,5-difluorobenzyl)-	<b>.</b>
		3-{[1-(3-	 
		ethynylphenyl)cyclopro	**574.3
	Ţ	pyl]amino}-2-	
	на	hydroxypropyl)-5-	
		methylbenzamide	
3319		hydrochloride	
		3 –	
1	1	{[butyl(methyl)amino]m	
	l l h h h	ethyl}-N-((1S,2R)-1-	
	N CF3	(3,5-difluorobenzyl)-	
	0 \\F	2-hydroxy-3-{[3-	**592.3
		(trifluoromethyl)benzy	
İ	. ⊧	1]amino)propy1)-5-	
2200	нся	methylbenzamide	
3320		hydrochloride	<u></u>

3321	Br OH H	3-bromo-5- {[butyl(methyl)amino]methyl}-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)benzamidehydrochloride	**638.2
3322	DH HZ FF FF FG	3- {[butyl(methyl)amino]methyl}-N-((15,2R)-1- (3,5-difluorobenzyl)- 3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-methylbenzamidehydrochloride	**578.4
3323	DH HZ F	(2R)-2-(4-buty1-3-oxopiperazin-1-y1)-N-((1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropyl}propanamide	
3324	H DH H N F F F F F F F F F F F F F F F F F	3- {[butyl(methyl)amino]methyl}-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5- methylbenzamide hydrochloride	**552.3
3325	N S H H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-6-(1,3-thiazol-2-yl)isonicotinamide	
3326	H OH H N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-3-{[isopentyl(methyl)amino]methyl}-5-methylbenzamidehydrochloride	**664.2

		·	
3327	H N N N N N N N N N N N N N N N N N N N	N-{(1S,2R)-1-(3-butoxybenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(methylsulfonyl)amino]-1,3-oxazole-4-carboxamide	**559.1
3328	N H OH H	3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}imidazo[1,2-a]pyridine-6-carboxamide	
3329	H H OH H N H F	2- [butyl(methyl)amino]- N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-6-(1,3- oxazol-2- yl)isonicotinamide	,
3330	H QH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-benzodioxole-5-carboxamide	**483.2
3333	H H OH H N N H F F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[methyl(propyl)amino]-6-(1,3-oxazol-2-yl)isonicotinamide	
3334	HCI	3- {[butyl(methyl)amino]methyl}-N-{(15,2R)-1- (3,5-difluorobenzyl)- 2-hydroxy-3-[(1- phenylcyclopropyl)amino]propyl}-5- methylbenzamide hydrochloride	**550.3

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3335	3-   ([butyl(methyl)amino]methyl)-N-{(1S,2R)-1-   (3,5-difluorobenzyl)-   2-hydroxy-3-[(3-   isopropylbenzyl)amino]   propyl}-5-   methylbenzamide   hydrochloride	**566.3
3337	3-   ([butyl(methyl)amino]methyl}-N-((1S,2R)-1-   (3,5-difluorobenzyl)-   3-{[1-(3-   ethynylphenyl)cyclopropyl]amino}-2-   hydroxypropyl)-5-(1,3-   oxazol-2-yl)benzamide   hydrochloride	**627.3
3339	3- {[butyl(methyl)amino]methyl}-5-cyano-N- ((1s,2r)-1-(3,5- difluorobenzyl)-3-{[1-(3- ethynylphenyl)cyclopropyl]amino}-2- hydroxypropyl)benzamide	**585.3
3342	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-furylmethyl)(methyl)amino]methyl}-5-methylbenzamidehydrochloride	**576 4
3343	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2-methoxyethyl)(methyl)amino]methyl}-5-methylbenzamidehydrochloride	**554.5
3344	3-{[[2- (diethylamino)ethyl](m ethyl)amino]methyl}-N- {(1s,2r)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5- methylbenzamide hydrochloride	

	Br Br	N-[(1S,2R)-3-[(3-bromobenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-2-	**457
3345	F	methoxyacetamide	
3346	H OH H OH H N N N N N N N N N N N N N N	formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[4-(ethoxymethyl)piperidin-1-yl]pentanamide(2:1)	,
3347 ~		N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-3-oxoindane-5-carboxamide	**493.2
3348	HO O F	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- hydroxyindane-5- carboxamide	**495.2
3349	HOH HOH	formic acid compound with N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(4-propoxypiperidin-1-yl)acetamide (2:1)	·
_	H OH H		**614.3
3350	O H OH H		
	Ö F		**628.3
3351	<u> </u>		

3352	HCI PER PER PER PER PER PER PER PER PER PER	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[isobutyl(methyl)amino]methyl}-5-methylbenzamidehydrochloride	**552.5
3353	H OH H OH N N N N	formic acid compound with 2-(1-buty1-2-oxopiperidin-4-y1)-N-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropyl}acetamide (1:1)	
3354	N O O O O O O O O O O O O O O O O O O O	formic acid compound with 2-(4-butylpiperazin-1-y1)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide (3:1)	
3355	l s ^	4-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide or ELAN157245	
	HZ FF	2-[(2S)-4-buty1-2- methy1-3-oxopiperazin- 1-y1]-N-{(1S,2R)-1- (3,5-diffuorobenzy1)- 3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}acetamid	
3357	Ha OH H	e hydrochloride  2-[(2R)-4-butyl-2- methyl-3-oxopiperazin- 1-yl]-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e hydrochloride	

	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-ethylbenzyl)amino	-[(3- ]-2-	
	N 0 F hydroxypropyl}-2-dioxo-4-		
3359	propylpiperazin-1-  F yl)acetamide  hydrochloride	-	
3333	H 4-butyl-N-{(1s,2R)		
•	H OH H (3,5-difluorobenzy)		
	ethylbenzyl)amino; hydroxypropyl}-	J-2-   **5	51
	1,2,3,4- tetrahydroquinoxa:	line-	
3360	F 6-carboxamide HCI hydrochloride		
	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-ethylbenzyl)aminohydroxypropyl}-3-	-[(3- ]-2-	
	methyl-5- {[methyl(pentyl)ar	**56	6.5
22.54	methyl}benzamide		
3361	hydrochloride N-{(1S,2R)-1-(3,5)		
	difluorobenzy1)-3- ethylbenzy1)amino hydroxypropy1}-3- {[(2R)-2-		0.4
	(methoxymethyl)py: din-1-yl]methyl}-! methylbenzamide		
3362	hg hydrochloride		
	N-((1S,2R)-1-(3,5-difluorobenzyl)-3		
	ethynylphenyl)cyc	ropro	
3363	hydroxypropyl)-2- (dipropylamino)iso	onico	
3363	tinamide F N <sup>1</sup> -{(1S,2R)-1-(3,5		
	difluorobenzyl)-3-		
	O O H [ (dimethylamino)mo		
	N N N N N N N N N N N N N N N N N N N	5-	39
3364	N N3, N3- dipropylisophthal		
	<u> </u>		

3365	S H H N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(dipropylamino)-4-methyl-1,3-thiazole-5-carboxamide	
3367		N-{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-3-phenyl-1H-thieno[2,3-c]pyrazole-5-carboxamide	
3368	H H OH H	N-((1S,2R)-1-(3,5-difluorobenzyl)-3- {[(4R)-6-ethyl-2,2-dioxido-3,4-dihydro-1H-isothiochromen-4-yl]amino}-2-hydroxypropyl)-3,5-dimethylbenzamide	**616.2
3370	Br QH H QH H N P F P P P P P P P P P P P P P P P P P	3-bromo-5- {[butyl(methyl)amino]methyl}-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}benzamid	
3371	H-Q-+-X	1-buty1-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-1H-indole-6-carboxamide	
3372	F O H, N N H H OH H	ALB 12052 or N <sup>1</sup> - {(1S,2R)-1-(3,5- difluorobenzyl)-3- [({4- [(dimethylamino)methyl] ]pyridin-2- yl}methyl)amino]-2- hydroxypropyl}-5-(1,3- oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	*663

3373	H H Z F F F F F F F F F F F F F F F F F	3- [(butylamino)methyl]- N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- nydroxypropyl}-5- methylbenzamide nydrochloride	**538.5
3374	H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-{[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-5-methylbenzamidehydrochloride	**580.4
3375	H OH H OH F	formic acid compound with N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[4-(2-methoxyethyl)piperidin-1-yl]acetamide (2:1)	
3376	HN QH H	1-butyl-N-{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxamide	**550.4
3377	F N N	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>1</sup> ,5- dimethyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3378	F	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[3-(dimethylamino)prop-1-ynyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	

	II II	N-{(1S,2R)-1-(3,5-	
		<pre>difluorobenzy1)-3-[(3- ethylbenzyl)amino]-2-</pre>	
	N Z N N	hydroxypropyl}-2-(2-	
		phenoxyphenyl)acetamid	
1		e	
1.	· F─ <b>⟨</b>		
3379	'		
	. OH	N-{(1S,2R)-1-(3,5-	
1	H OH H C	difluorobenzyl)-3-[(3-	
İ		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-(2,5-	
	_ /=\	dimethylphenyl)acetami	
		đe	
	F		
3380	,		
	F	N-{(1S,2R)-1-(3,5-	
	F O J OH J	difluorobenzyl)-3-[(3-	
	F N PH N	ethylbenzyl)amino]-2-	
	I LA JŽHOO	hydroxypropy1}-2-[2-	
	l l l l	(trifluoromethoxy)phen	
		yl]acetamide	
	' 🖳		
	F		
3381			
		N-{(1s,2r)-1-(3,5-	
	P H PH H	difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2-	
	N N N	hydroxypropyl}-2-(2-	
		ethoxyphenyl)acetamide	
		conoxypiony 1, december	
	F—( )		
2200	F		
3382	l F	N-{(1S,2R)-1-(3,5-	
	F F OH	N-{(18,28)-1-(3,5- difluorobenzyl)-3-[(3-	
	H SHH	ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-[2-	
	" Ö	(trifluoromethyl)pheny	
-	_ /=<	l]acetamide	
	F—	7	
	F		
3383	•		
	O OH	N-{(1S,2R)-1-(3,5-	
	H OHH	difluorobenzyl)-3-[(3-	
1		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-2-(2-	
		methoxyphenyl)acetamid	
		е	
	F.		
3384	<u> </u>		

	<del></del>	<del></del>	
	O H QH H	2-[2- (benzyloxy)phenyl]-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e	
3385			
2206	O H H N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylbutanamide	
3386		7 (/1 ( 0 0 0 ) 1 / 2 ( 0 0 0 )	
3387	H N H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-mesitylacetamide	
	O 11 OH 11	N-{(1S,2R)-1-(3,5-	-
	H N	<pre>difluorobenzyl) -3-[(3- ethylbenzyl) amino]-2- hydroxypropyl}-2-(2,4- dimethoxyphenyl) acetam ide</pre>	
3388		0 (0 -1-11) 27	
3389	F F	2-(2-chlorophenyl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e	
	., OH	2-cyclohexyl-N-	
3390	H OHH H N	{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}acetamide	
2220	l		

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1		ELAN-157393	
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3391	F		
	· ·	ELAN-157394	
	TH OH		
	TOH H OH H		
	• H X ··· H		
	F{ }		
3392	F		
		2-cyclopent-2-en-1-yl-	
		N-{(1S, 2R)-1-(3,5-	
		difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2-	
		hydroxypropyl}acetamid	:
		e	
	F—( )		
3393			
5555	, s	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
•	O NH OH H	ethylbenzyl)amino]-2-	
	N TH N	hydroxypropyl}-2-(1- methyl-5-oxo-2-	
	∥ ∮ H	thioxoimidazolidin-4-	
		yl)acetamide	
	F—( )		
	F		
3394		•	
* * * *	F H PH H	N-{ (1s, 2r) -1- (3, 5-	
		difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2-	
	H H	hydroxypropy1}-2-(2-	
	<sub>F</sub>	fluorophenyl)acetamide	
	· <b>\</b>		
3395	) F		
	OH	2-cyclopropyl-N-	
	H OH H	{ (1S,2R)-1-(3,5-	
	A THOUSE	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}acetamid	
		e.	
	<u>"-</u> {_		
3396	, , <del>,</del>		
	<u> </u>	L	L

3397	H OHH H N	2-cyclohex-1-en-1-yl- N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid e	
3398	H QH H N H N H	2-(1-adamanty1)-N- {(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropyl}acetamid e	
3399	H OH H	(2S)-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- phenylpropanamide	
	H OH H N H	(2R)-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- phenylpropanamide	
3400		2-(2,4- dichlorophenyl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}acetamid	
3402	F H N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2,3-dimethoxyphenyl)acetamide	,

3403	P P P P P P P P P P P P P P P P P P P	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[3-(dimethylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
3403	Ę	N <sup>1</sup> -((1S,2R)-1-(3,5-	
	P HOH H	difluorobenzyl)-3-{[1-(4-ethynylpyridin-2-yl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
3406			
3407		4-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,4-dihydro-2H-1,4-benzothiazine-6-carboxamide 1-oxide	:
3408	HO OH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-heptyl-4-hydroxy-L-prolinamide	
2400	Cl	2-	
3409	N O H N F F	[butyl(methyl)amino]-6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide	
7=07	■N	2-	
3410	H OH H N F	[butyl(methyl)amino]-6-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}isonicotinamide	
	<del></del>		<u></u>

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	F	ALB-12164 N'-{(1s,2r)-1-(3,5-	
	F	difluorobenzyl)-3-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	[({2-	
•		[(dimethylamino)methyl	4.550
	I I H HOH H	]pyridin-4-	*663
		yl}methyl)amino]-2-	
•	, N V	hydroxypropyl}-5-(1,3-	
		oxazol-2-yl)-N,N-	
3411		dipropylisophthalamide	
		4-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-	
	5	3-[(3-	
		ethylbenzyl)amino]-2-	
•	<u></u>	hydroxypropyl}-8-(1,3-	
	0. cN	oxazo1-2-y1)-3,4-	<u>.</u>
		dihydro-2H-1,4-	
1	H OH H	benzoxazine-6-	
1		carboxamide or 4-	**619
		butyl-N-{(1s,2r)-1-	
		(3,5-difluorobenzyl)- 3-[(3-	
		ethylbenzyl)amino]-2-	
	F	hydroxypropyl}-8-(1,3-	
		oxazo1-2-y1)-3,4-	
		dihydro-2H-1,4-	,
		benzoxazine-6-	
3412		carboxamide	
	O_N	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-(4-	
		ethyl-1,3-oxazol-2-	**601
		yl)-5-(1,3-oxazol-2-	001
		yl)benzamide	
	, на ў	hydrochloride	
3413	٢		
	·· · - <u>-                              </u>		
	HO		*****
			**540.4
	<u> </u>		
3414	r Ka		
	Br		
1		•	
			**656.2
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3415	1104		ì

3416	H DH H	3-benzyl-4-(4-butylphenyl)-N- {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxobutanamide	**641.6
3417	H-CI H-CI	2-(4-buty1-2- oxopiperazin-1-y1)-N- {(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}acetamid e dihydrochloride	
3418		N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[4-(ethoxymethyl)piperidin-1-yl]acetamide	
	O N O H N F H N H N F F H N H N H N H N H N H	2-(4-buty1-2,3-dioxopiperazin-1-y1)-N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethy1benzy1)amino]-2-hydroxypropy1}hexanamide hydrochloride	
3419	н нон н	N <sup>1</sup> -((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(4-ethynylpyridin-2-yl)cyclopropyl]amino}-2-hydroxypropyl)-5-(1,3-oxazol-2-yl)-N <sup>3</sup> ,N <sup>3</sup>	
3422	OH OH F	5-[((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethylphenyl)cyclopropyl]amino}-2-hydroxypropyl)amino]-5-oxopentanoic acid	**475.2
3423	H OH H	1-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2,3,4-	

		tetrahydroquinoline-7-	·
		carboxamide or 1-	ļ
		butyl-N-{(1S,2R)-1-	
1			
		(3,5-difluorobenzyl)-	
		3-[(3-	
		ethylbenzyl)amino]-2-	
ŀ		hydroxypropyl}-	
		1,2,3,4-	
		tetrahydroquinoline-7-	
		carboxamide	
	O H OH H	4-[((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-{[1-	
	HO NY VIII	(3-	
<b>.</b> .		ethylphenyl)cyclopropy	
		1]amino}-2-	**461.2
	· •		
	·	hydroxypropyl)amino]-	
1	Ė	4-oxobutanoic acid	
3424			L
	0.	N-{(1S,2R)-1-(3,5-	
1		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
	1 / 11 = 1		1
1		hydroxypropyl}-3-	i
		propyl-1,2-	
1		benzisoxazole-5-	,
3425	ļ	carboxamide	
	N/S	2-	
	H ÔH H	[allyl(methyl)amino]-	· .
	N, N, N, N, N, N, N, N, N, N, N, N, N, N	1	
		N-{ (1S, 2R) -1-[3-	
	\	(allyloxy)-5-	**5 <b>4</b> 7.5
		fluorobenzyl]-3-[(3-	547.5
1	" 0 1	ethylbenzyl)amino]-2-	1
		hydroxypropyl}isonicot	
	Į · F	inamide	
3426			
	н он н	1-allyl-N-{(1S,2R)-1-	
		[4-(allyloxy)-3-	,
		fluorobenzyl]-3-[(3-	1
1 .		ethylbenzyl)amino]-2-	
		hydroxypropyl}-1H-	**556.4
	4/		· · · · · ·
		indole-6-carboxamide	
		1	
2427	F		
3427		1 (/10 00) 1 (0 0	<del> </del>
		N-((1S,2R)-1-(3,5-	
}		difluorobenzyl)-3-{[1-	1
	N N H OHH	(3-	Į.
1	N N N N N N N N N N N N N N N N N N N	ethynylphenyl)cyclopro	1
1	I H A	pyl]amino}-2-	
		hydroxypropyl)-4-	
1	// <b>∀</b> F		
1		phenyl-2-(1H-pyrrol-1-	
1	<u></u>	yl)-1,3-thiazole-5-	
3428	,	carboxamide	
. I M / C D	i .	1	1

	<del></del>		
		N-((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1-	
	1	(3-	
		ethynylphenyl)cyclopro	
		pyl]amino}-2-	
		hydroxypropyl)-2-	
	<u> </u>	(dipropylamino)-4- (trifluoromethyl)-1,3-	
3429		thiazole-5-carboxamide	
3423		N-((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-{[1-	
	N //	(3-	
		ethynylphenyl)cyclopro	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	pyl]amino}-2-	
		hydroxypropyl)-2,6- dimorpholin-4-	
		ylpyrimidine-4-	
		carboxamide	
	F		
	l Ý l		
3432	F		: '
3432		N-{(1S,2R)-1-(3,5-	*
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-	
	<b>/</b>	{ [ (2S) -2-	
		ethylpyrrolidin-1-	
		yl]carbonyl}-5-	
3433	I F I	methylbenzamide hydrochloride	
3 4 3 3		(2S)-2-(4-buty1-3-	
		oxopiperazin-1-yl)-N-	,
		{ (1S, 2R) -1- (3, 5-	
		difluorobenzyl)-3-[(3-	
	I 11 I I	ethylbenzyl)amino]-2-	
		hydroxypropyl}propanam	
3434	L	ide hydrochloride	
	l <b>-</b>	N-((1S,2R)-1-(3,5-	
	1 ' <i>1</i> 1	difluorobenzyl)-3-{[1- (3-	
	H OH H	ethynylphenyl)cyclopro	
		pyl]amino}-2-	
	l !! ÷*(; /\ [	hydroxypropyl)-1-	
	F	methy1-3-	
		(trifluoromethyl)-1H-	
[		thieno[2,3-c]pyrazole-	
3451	· \	5-carboxamide	

3452	N N N N N N N N N N N N N N N N N N N	2- [allyl(methyl)amino]- N-{(1S,2R)-1-[4- (allyloxy)-3- fluorobenzyl]-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}isonicot inamide	**547.4
3453	N N N N N N N N N N N N N N N N N N N	3-butyl-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,2-benzisoxazole-5-carboxamide	**536
	N H H OH H	5-(3-aminopropyl)-N <sup>1</sup> - {(1s,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3454	F HN N H	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[3-(methylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide or ELAN157961	
	L ZH H	N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-[3- (methylamino)prop-1- ynyl]-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	
3456	O N H OH H	5-(3-aminoprop-1-ynyl)-N1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N3,N3-dipropylisophthalamide or ELAN157963	

3458	N O OH HN NH	N-((1S,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-5-pyrrolidin-1-ylpyrazine-2-carboxamide	
3459	Q (JH	4-butoxy-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}quinoline-2-carboxamide	
3461	N H OH H N F F	2-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-[methyl(propyl)amino]isonicotinamide	
3462	H QH H N N N N N N N N N N N N N N N N N	3-acetyl-1-butyl-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1H- indole-6-carboxamide	· ·
3462		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(1H-indol-6-ylmethyl)amino]propyl}-5-methyl-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	**591.5
3464	OH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-isobutyl-1,2-benzisoxazole-5-carboxamide	**536

		- 4 (4 - 4 - 14 - 14 - 14 - 14 - 14 - 14	
		N-{(1S,2R)-1-(3,5-	
	HN OU	difluorobenzyl)-3-[(3-	i
	H H OHHH	ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	
		[(2S)-pyrrolidin-2-	
		yl]acetamide	
	<i>/</i> ≕⟨	, 1, account ac	
	F( )		İ
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3465	F		
		2-[2-({(1s,2r)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	ì
		hydroxypropyl}amino)-	
		2-oxoethyl]-N-(6-	
		methoxypyridin-3-	į
	HN O "OH "	yl)benzamide	
		·	
1	N N		
	Y		
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3466			
	F	2-[2-({(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}amino)-	
	I I II HA	2-oxoethyl]-N-(2,4-	
]	N N N N N N N N N N N N N N N N N N N	difluorophenyl)benzami	
	X	de	
	HN O	ue .	
Į.	F		
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3467			
	F	N-{(1S,2R)-1-(3,5-	
1	· 🙏	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	'
		hydroxypropyl}-2-	
	H,	pyridin-3-ylacetamide	[-····· ·
1			
	H H OH H	İ	] ,
2460			
3468	F	N-{(1S,2R)-1-(3,5-	
	Γ		[
1		difluorobenzyl) -3-[(3-	]
		ethylbenzyl)amino]-2-	
	NH O	hydroxypropyl}-2-(1H-	
	NJ IN A A A A	imidazol-5-	
1	I V N N Y N	yl)acetamide	
	HH, OH H		
2460			
3469			<u> </u>

• ,			
3470	O H, N H OH H	2-cyclopenty1-N- {(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropyl}acetamid e	
3471	OH, NHOH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-hydroxyphenyl)acetamide	
3472	O H, F N H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-methylphenyl)acetamide	
3473	F N H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2-iodophenyl)acetamide	
	O H, F N H H OH H	1-(4-chlorophenyl)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5- oxopyrrolidine-3- carboxamide	
3474 3475	CI O H, N H H OH H	4-(2,4- dichlorophenoxy)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}butanami de	,

I			
3476	F F	4,5-dibromo-N- {(1s,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}thiophen e-2-carboxamide	
3477	P H	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetamide	
3478	N N O OH NH	N-((1s,2R)-1-(3,5-difluorobenzyl)-3-{[1-(3-ethynylphenyl)cyclopropyl]amino}-2-hydroxypropyl)-2,6-bis(dimethylamino)pyrimidine-4-carboxamide	
3479	DH HN F	4-butyl-8-cyano-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3,4- dihydro-2H=1,4- benzoxazine-6- carboxamide	**577
3480	H OH H N N N F F	3-(allylsulfonyl)-N- ((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethylphenyl)cyclopropy 1]amino}-2- hydroxypropyl)benzamid e	

	н бин	3-(allylthio)-N-	ı
		((1S,2R)-1-(3,5-	, ,
		difluorobenzyl)-3-{[1-	
	Ö 🛔 🚾 '	(3-	= = =
		ethylphenyl)cyclopropy	**537.8
	41		
1		1]amino}-2-	
	Ė	hydroxypropyl)benzamid	l
3481		e	
	0	formic acid compound	
		with N1-[(3S)-1-	
	*, -,,	azabicyclo[2.2.2]oct-	
			` '
1	H OH H	$3-y1]-N^5-((1s,2R)-1-$	
		(3,5-difluorobenzyl)-	**583.3
}	NH	3-{[1-(3-	
1		ethylphenyl)cyclopropy	
<u>'</u>		1]amino}-2-	
	`N'	hydroxypropyl)pentaned	İ
h 404			
3484		iamide (1:1)	
		formic acid compound	
	н∼он	with N <sup>1</sup> -[(3R)-1-	
		azabicyclo[2.2.2]oct-	
*.	L OH L	$3-y1]-N^5-((1S,2R)-1-$	
		(3,5-difluorobenzyl)-	ļ i
	NH O	3-{[1-(3-	**583.3
	NH U F		
1	[4]	ethylphenyl)cyclopropy	j
	N Y	1]amino}-2-	
	F	hydroxypropyl)pentaned	
3485		iamide (1:1)	
	Q	formic acid compound	
	н Дон	with N1-[(3S)-1-	}
	,, 5,,	azabicyclo[2.2.2]oct-	1
1	OH (*)	3-y1]-N <sup>4</sup> -((1s,2R)-1-	
			-
	I WH WINT WINT WAS A	(3,5-difluorobenzyl)-	**569.3
	[4]	3-{[1-(3-	
1	N   Y   Y	ethylphenyl)cyclopropy	-
1	\ <u>\</u>	1]amino}-2-	ļ
}		hydroxypropyl) succinam	
3486		ide (1:1)	
		formic acid compound	<del> </del>
-			1
1	HOH	with N <sup>1</sup> -[(3R)-1-	İ
1		azabicyclo[2.2.2]oct-	
		$[3-y1]-N^4-((1s,2R)-1-$	
1		(3,5-difluorobenzyl)-	**569.3
1		3-{[1-(3-	7.209.3
1	[ ] \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	ethylphenyl)cyclopropy	1
· ·	"	l]amino}-2-	
1	Ţ		
L	F.	hydroxypropyl) succinam	
3487	1	ide (1:1)	1

		1 244 - 0 - 1 40 - 5	
l		$N^{1} - \{ (1s, 2R) - 1 - (3, 5 - 1) \}$	
	Y W	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-5-[4-	
		(dimethylamino)but-1-	
ļ †	rr	$yny1]-N^3,N^3-$	ì
	1 1	dipropylisophthalamide	
	Ψ <u>\</u> .	or ELAN158095	1
.	· · · · · · · · · · · · · · · · · · ·		
3490		1 1 1 2 2 (/10 00) 1	
		1-butyl-N-{(1S,2R)-1-	
1	~ H OH (~ ? )	(3,5-difluorobenzyl)-	
		3-[(3-	i
	\ II = 1	ethylbenzyl)amino]-2-	
	0 \	hydroxypropyl}-3-	
		(trifluoroacetyl)-1H-	
		indole-6-carboxamide	
	<u> </u>		
3491			
		N-((1S,2R)-1-(3,5-	
ŀ	1	difluorobenzyl)-3-{[1-	
	л ф н Он н С	(3-	
		ethynylphenyl)cyclopro	
		pyl]amino}-2-	**588.3
		hydroxypropyl)-3-	566.5
	Ţ	{[isopentyl(methyl)ami	
	, HG	no]methyl}-5-	
	·	methylbenzamide	
3492		hydrochloride	
		N-((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-{[1-	
	H QH H	(3-	
		ethylphenyl)cyclopropy	
	Ö	1]amino}-2-	  **592.3
		hydroxypropyl)-3-	3,2.3
1	Ĭ	{[isopentyl(methyl)ami	1
	нс	no]methyl}-5-	
		methylbenzamide	
3493	·	hydrochloride	
		N-((1s,2R)-1-(3,5-	
	M H OH H	difluorobenzyl)-3-{[1-	
		(3-	
1		ethynylphenyl)cyclopro	
1	F	pyl]amino}-2-	
		hydroxypropyl)-4-	
1	/ F	(dipropylamino)-1-	
1	·	methyl-1H-pyrrole-2-	1
		carboxamide ·	

1	l I	N-((1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	1
1	11 1 1 1 1 1	{[(4R)-6-ethyl-2,2-	1
1		dioxido-3,4-dihydro-	
		1H-isothiochromen-4-	
1	() 1	yl]amino}-2-	
		hydroxypropyl)-4-(2-	
	Ť	methoxyethyl)benzamide	
L	F		
3495		-1 ((1 0 0 0 ) 1 (2 5	
1		$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
1		difluorobenzyl)-3-[(3-	j
		ethylbenzyl)amino]-2-	ļ
		hydroxypropy1}-5-[4-	
	N TO N HON N TO	(dimethylamino)butyl]-	
	Y Y	N <sup>3</sup> , N <sup>3</sup> ~	, 1
		dipropylisophthalamide	l
	LN	or ELAN158113	
3496			l
	NI	ELAN-158116	
1	\( \times \)		
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	HN. Ž NH		
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		. '	
2407	<u>l</u>		
3497	<u> </u>	ELAN-158128	
	CI ///	1	
ļ		2,6-dichloro-N-	
		((1 <i>S</i> , 2 <i>R</i> ) -1-(3, 5-	
	CI N OH	difluorobenzyl)-3-{[1-	, ]
	HN. NH	(3-	
		ethynylphenyl)cyclopro	
		pyl]amino}-2-	
1		hydroxypropyl)pyrimidi	
]		ne-4-carboxamide	• • •
2500	<u> </u>		
3500	<u> </u>	N-((1S,2R)-1-(3,5-	
	<b> </b>		
1	N H H OH H	difluorobenzyl)-3-{[1-	•
		(3-	
		ethynylphenyl)cyclopro	
		pyl]amino}-2-	
1		hydroxypropyl)-2-	
1	<b>/</b>	morpholin-4-yl-4-	
1	Į F	(trifluoromethy1)-1,3-	
3503		thiazole-5-carboxamide	

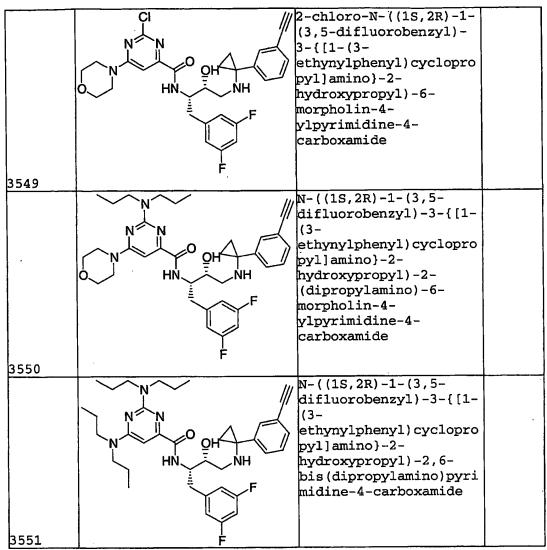
3506	S H H H H H H H H H H H H H H H H H H H	· · .	**688
3507	DH H N N N N N N N N N N N N N N N N N N	N <sup>1</sup> -[(1S,2R)-1-(3,5- difluorobenzyl)-3- ({[1-(3-ethylphenyl)- 1H-tetraazol-5- yl]methyl}amino)-2- hydroxypropyl]-5- methyl-N <sup>3</sup> ,N <sup>3</sup> - dipropylisophthalamide	**648
3508	O'S H OH H	3-(allylsulfinyl)-N- ((1s,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethylphenyl)cyclopropy 1]amino}-2- hydroxypropyl)benzamid e	**553.8
	F OH H OH H	N <sup>1</sup> -{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[3-(dimethylamino)propyl]-N <sup>3</sup> ,N <sup>3</sup> -dipropylisophthalamide	
3520	HO F F N N N N N N N N N N N N N N N N N	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)aminol-2-hydroxypropyl}-3'-(hydroxymethyl)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3522	N H H OH H	3'-cyano-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	

3523	P P P P P P P P P P P P P P P P P P P	N-((1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2'-ethoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3524	F N H OH H	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-thiazol-2-yl)-3'-(trifluoromethoxy)-1,1'-biphenyl-3-carboxamide	
3525	P F N N N N N N N N N N N N N N N N N N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4'-propoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	i .
3526		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4'-(dimethylamino)-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3527	H H OH H	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2'	
3528		N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3'-propoxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	

		N-{(1s,2r)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
	\	ethylbenzyl)amino]-2-	
	PH <sub>M</sub> F	hydroxypropyl}-3'-	
		ethoxy-5-(1,3-thiazol-	
l i	(	2-y1)-1,1'-biphenyl-3-	
	<u> </u>	carboxamide	
	NI C	Carboxamide	
	NS		
3529	_		
	F	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	1
	1 1	ethylbenzyl)amino]-2-	
		hydroxypropyl}-4'-	ļ
	1	ethoxy-5-(1,3-thiazol-	
	""OH"	_	ļ
	NI e	2-y1)-1,1'-biphenyl-3-	
		carboxamide	
3530	<u> </u>		
	F	N-{(1S,2R)-1-(3,5-	. 7
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-4'-	
	N H OH H	isopropoxy-5-(1,3-	
		thiazol-2-yl)-1,1'-	
	N∕s	biphenyl-3-carboxamide	İ
	\ <u></u>	prometrial-3-carboxamide	· i
3531			
	Ī	N-{(1S,2R)-1-(3,5-	:
		difluorobenzyl)-3-[(3-	•
	0 F	ethylbenzyl)amino]-2-	
	H. H.	hydroxypropyl}-4'-	
	L HHOH H L	(hydroxymethyl)-5-	
	Y • • • •	(1,3-thiazol-2-yl)-	,
1	N N S	1,1'-biphenyl-3-	
250	\/	carboxamide	
3532			
	1	4'-butoxy-N-{(1S,2R)-	
		1-(3,5-,	:
	I HOUSE	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-5-(1,3-	• • • • • • • • • • • • • • • • • • •
1	N/s	thiazol-2-y1)-1,1'-	
1		biphenyl-3-carboxamide	
3533			
	Į	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-4'-	
		methoxy-5-(1,3-	
	H. OH H	thiazol-2-yl)-1,1'-	
	」 .人	biphenyl-3-carboxamide	· ·
	NS	brbitettar-2-carpovamine	
3534			
	<u> </u>		

	<del></del>		
3535	F F F F F F F F F F F F F F F F F F F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-thiazol-2-yl)-4'-(trifluoromethoxy)-1,1'-biphenyl-3-carboxamide 4'-butyl-N-{(1s,2r)-1-	
3536	H, F N H OH H	(3,5-difluorobenzyl) - 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-(1,3- thiazol-2-yl)-1,1'- biphenyl-3-carboxamide	
3537	F H, N, H, OH N, H, OH N, H, OH	3'-butoxy-N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3538	H H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3'-isopropyl-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3539	NH OH H	3'-(acetylamino)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[-(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-(1,3- thiazol-2-yl)-1,1'- biphenyl-3-carboxamide	
3540	O H. N H OH H	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2'-methyl-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	

3541	P H H OH H	2'-acetyl-N-{(1S,2R)- 1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-(1,3- thiazol-2-yl)-1,1'- biphenyl-3-carboxamide	
3542	HO O H, F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4'-hydroxy-5-(1,3-thiazol-2-yl)-1,1'-biphenyl-3-carboxamide	
3543	H H OH H	4'-(acetylamino)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-5-(1,3- thiazol-2-yl)-1,1'- biphenyl-3-carboxamide	
		N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1H-pyrrol-2-yl)-5-(1,3-thiazol-2-yl)benzamide	,
3544		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(E)-2-(4-fluorophenyl)ethenyl]-5-(1,3-thiazol-2-yl)benzamide	
3546	N H OH H N F F	N-((1S,2R)-1-(3,5- difluorobenzyl)-3-{[1- (3- ethynylphenyl)cyclopro pyl]amino}-2- hydroxypropyl)pyrimidi ne-4-carboxamide	



\* means M/Z (EI)

\*\* means M+H (CI)

\*\*\* means OAMS

\*\*\*\* means MS Data

CHART A

$$H_{2}N \longrightarrow OH \longrightarrow PG \longrightarrow PG \longrightarrow PG \longrightarrow H \longrightarrow PG \longrightarrow H_{1} \longrightarrow H_{2} \longrightarrow PG \longrightarrow H_{1} \longrightarrow H_{2} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{2} \longrightarrow H_{3} \longrightarrow H_{3} \longrightarrow H_{4} \longrightarrow$$

(X)

CHART B

$$X_1$$
 $R_2$ 
 $R_3$ 
 $(VI)$ 
 $R_2$ 
 $R_3$ 
 $(VII)$ 
 $R_3$ 
 $R_4$ 
 $R_5$ 
 $R_6$ 
 $R_6$ 
 $R_7$ 
 $R_8$ 
 $R_8$ 
 $R_8$ 
 $R_8$ 
 $R_8$ 
 $R_8$ 

PG = protecting group X<sub>1</sub> is a leaving group

PG = protecting group X<sub>1</sub> is a leaving group

5

## CHART C

(III)

$$PG \xrightarrow{H} PG \xrightarrow{R_3} PG \xrightarrow{H} PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1} R_2 R_3 PG \xrightarrow{R_1}$$

# CHART D

## CHART E

5

# **CHART F**

$$\begin{array}{c} OH \\ R_{N-a}O \\ OKXIV) \end{array} \qquad \begin{array}{c} O-SO_2-CF_3 \\ R_{N\alpha} \\ OR_{N-a} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ OR_{N-a} \end{array} \qquad \begin{array}{c} OR_{N-a} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \\ R_{N\alpha} \end{array} \qquad \begin{array}{c} R_{N\alpha} \\ R_$$

# **CHART G**

$$\begin{array}{c} NO_2 \\ R_{N-a}O \\ O \\ (XXVIII) \end{array} \\ OH \\ R_{N-a}O \\ (XXIX) \\ (XXIX) \\ OR_{N-a} \\ R_{N-a}O \\ (XXXI) \\ OR_{N-a} \\ R_{N-a}O \\ (XXXI) \\ (XXXII) \\ (XX$$

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$$\begin{array}{c|c} & & & & \\ \hline R_{N\alpha} & & & & \\ R_{N\beta} & & & & \\ \hline \end{array}$$

# CHART I

# **CHART J**

# **CHART K**

# CHART L

$$CO_2H$$

$$O_2N$$

$$(XLIII)$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

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$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Benzyl})$$

$$O-(Alkyl \text{ or Be$$

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# **CHART M**

# **CHART N**

$$\begin{array}{c} R_{N\alpha} \\ R_{N\beta} \\ O \\ (XXI) \end{array} \longrightarrow \begin{array}{c} R_{N\alpha} \\ R_{N\beta} \\ O \\ (IX-LII) \end{array} \longrightarrow \begin{array}{c} R_{N\alpha} \\ O \\ (IX-LII) \\ O \\ \end{array}$$

# **CHART O**

$$(C_1 \cdot C_4) \text{alikyl} - O + (C_1 \cdot C_4) \text{alikyl} - O +$$

(LXII)

# CHART P

# **CHART Q**

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# **CHART R**

$$(alkyl) - O + (Cl \text{ or } Br) + (alkyl) - O + (Cl \text{ or } Br) + (alkyl) - O + (Cl \text{ or } Br) + (alkyl) - O + (Cl \text{ or } Br) + (alkyl$$

# **CHART S**

$$\begin{array}{c} OH \\ H_2N/_{III} \\ CH \\ R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_7 \\ R_8 \\ R_8 \\ R_9 \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{2} \\ R_{3} \\ R_{3} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{3} \\ R_{3} \\ R_{4} \\ R_{5} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{5} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{5} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{8} \\ R_{1} \\ R_{2} \\ R_{3} \\ R_{5} \\ R_{6} \\ R_{6} \\ R_{7} \\ R_{8} \\ R_{$$

(XXXI)

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# $\begin{array}{c} \text{CHART T} \\ \\ \text{R}_{\text{N-a}}\text{O} \\ \\ \text{NH}_{2} \\ \\ \text{NH}_{\text{Na}}\text{R}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \text{NH}_{\text{Nb}} \\ \\ \\$

# CHART U

CHART U details a method for the preparation of ketones used in the invention. The preferred halogen is bromine or

iodine. A commercially available halogenated benzoate is coupled with  $(\alpha$ -ethoxyvinyl)-tributyl in the presence of a catalyst, for example a palladium catalyst like dichlorobis (triphenylphosphine)palladium, yielding a methylketone-5 substituted benzoate ester after hydrolytic workup. In a preferred embodiment of the invention, this reaction is conducted in an anhydrous organic solvent. In a further more preferred embodiment of the invention, this reaction is conducted in anhydrous toluene. (Kosugi and Migita, Bull. Chem. 10 Soc., Jpn., 1987, 60, 767-768). Base-catalyzed nucleophilic addition to a stoichiometric excess of alkyl'-LG (or alkyl"-LG) yields a symmetric dialkylated productthat, depending on the strength of the base, may be directly converted to the equivalent benzoate. Alternatively, the methylketone-15 substituted benzoate ester may be reacted with a lower excess of alkyl'-LG, yielding a mono-substituted derivative. Said derivative may be further alkylated by base-catalyzed reaction with alkyl"-LG. It is understood that LG is Leaving Group as defined above. It is understood by one skilled in the art how 20 to perform alkylations. In a preferred embodiment of the invention, said alkylations are catalyzed by sodium hydroxide or potassium hydroxide. In an additional preferred embodiment of the invention, the alkylations are conducted in a dipolar

aprotic solvent, e.g. dimethylsulfoxide.

# <u>CHART V</u>

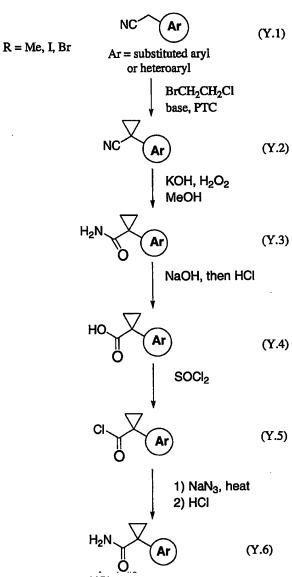


CHART V. Synthesis of 3-substituted
cyclopropylbenzylamines and related heteroaryl amines (Y.6 in
5 Chart V). A commercially available 3-substituted
benzylonitrile is reacted with 1-bromo-2-chloroethanein the
presence of an aqueous base and a phase transfer catalyst to
yield the a cyclopropanated benzylnitrile (Y.2). The cyanide
(Y.2) is converted to amide (Y.3), which is treated with
10 aqueous base, yielding acid (Y.4) after acidic workup. Acid
(Y.4) is converted to acyl chloride (Y.5), which is reacted

with azide, yielding an intermediate which undergoes rearrangement and decomposition to give product(Y.6). (Y.6) is then reacted according to Chart JJ to yield inhibitor (X). Representative procedures are provided in Example 2353.

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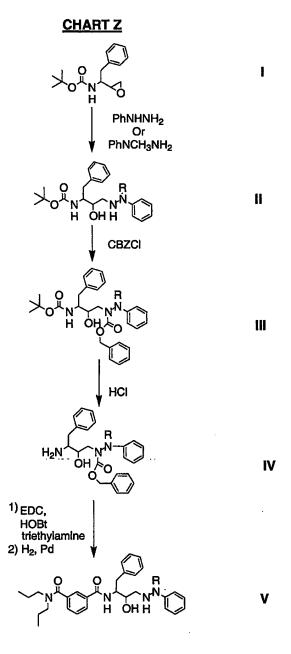


Chart Z. Reaction of epoxide I with an aromatic hydrazine in isopropanol produces the selective alkylation of the unsubstituted hydrazine nitrogen, yielding hydrazine II (M.

Nakakata, Tetrahedron Letters 1993, 6095-6098). Acylation of one of the hydrazine nitrogens with an acylating agent, e.g. benzyloxycarbonyl, yields III and reduces the reactivity of this moiety to further acylation irrespective of which bydrazine nitrogen is the first to undergo acylation (B. Gisin, Helv. Chim. Acta 1970, vol 53, 1030-1043. S. Shinagawa, Chem. Pharm. Bull. 1981, vol 29, 3630-3638). Removal of the tert-butoxycarbonyl protecting group of III yields free amine IV, which is coupled to isophthalic acid (XIV)using carbodimide or other known coupling agents. Deacylation of the hydrazine nitrogen yields compound V.

CHART AA procedure:

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Selective acylation of methylhydrazine on the substituted nitrogen (D. Butler, *J. Medicinal Chemistry* **1971**, vol. 14, 1052-1054) yields acylhydrazine **VI**, which is reacted withwith

epoxide I in isopropanol to form adduct VII (S. Wang, J. Medicinal Chemistry 1997, vol 40, 937-941. G. Bold, J. Medicinal Chemistry 1998, vol 41, 3387-3401). Removal of the tert-butoxycarbonyl protecting group, followed by coupling to isophthalic acid (XIV) yields final product IX.

## 10 Chart BB procedure:

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Epoxide X is reacted with 0-benzylhydroxylamine to yield adduct XI (S. Rosenberg, J. Medicinal Chemistry 1990, vol 33, 1582-1590). Removal of the tert-butoxycarbonyl protecting group, followed by acylation with isophthallic acid XIV yields target compound XIII.

## **CHART CC**

Chart CC. Aniline XXXI is acylated with acyl chlorides or anhydrides or sulfonated with sulfonyl halides or sulfonyl anhydrides to yield sulfonamide-I using methods well known to those skilled in the art. Sulfonamide-I is alkylated with RX, wherein X is a leaving group, for example Cl, Br, tosylate, or mesylate, in the presence of a base, e.g. trialkylamine, sodium hydride, pyridine, or potassium t-butoxide, to yield sulfonamide-II.

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## **CHART DD**

Chart DD. Amine-a is acylated with acyl chlorides or anhydrides or sulfonated with sulfonyl halides or sulfonyl anhydrides to yield sulfonamide-I using methods known to those skilled in the art. Sulfonamide-Ia is alkylated with RX, wherein X is a leaving group, for example Cl, Br, tosylate, or mesylate, in the presence of a base, e.g. trialkylamine, sodium hydride, pyridine, or potassium t-butoxide, to yield sulfonamide-IIa.

**CHART EE** 

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Chart EE. Iodo amide (I) is coupled to a thiol RSH in the presence of a catalyst, for example a palladium (0) catalyst like bis(dibenzylideneacetone) palladium (0), an additive, preferably 1,1'-bis (diphenylphosphino) ferrocene, and a base, e.g. a trialkyamine, in an organic solvent, for example N-methylpyrrolidinone (NMP) or DMF, at a temperature ranging from room temperature to reflux temperature to yield sulfide (II). Sulfide (II) is oxidized with hydrogen peroxide in the presence of an acid or with a peracid, e.g. mchloroperoxybenzoic acid to yield sulfone (III). Other methods of oxidation are reported in references like Smith and March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed., Wiley Interscience, 2001. If sulfone (III) is an ester, it is further hydrolyzed to yield a carboxylic acid (IV, not shown) by basic hydrosolisis with a base like lithium, sodium, or potassium hydroxide, followed by acidic workup. Acid (IV) is then coupled to an amine to yield the final target product.

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## **CHART FF**

Chart FF. A halogenated benzyl-derivative of structure(1). (1)

25 is reacted with thiolate, for example a lithium, sodium or
potassium thiolate, in an organic solvent, for example THF,
toluene, or acetonitrile, at temperatures ranging from room
temperature to reflux, yielding a sulfanyl derivative of
structure(2). (2) is peroxidated with an oxidant, for example

30 hydrogen peroxide in the presence of an acid like acetic acid

or m-chloroperoxybenzoic acid, in an organic solvent like dichloromethane to yield methylene sulfone (3). Other methods of oxidation are reported in references like Smith and March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5<sup>th</sup> Ed., Wiley Interscience, 2001. If necessassary, sulfone (3) is hydrolyzed to its acid derivative by methods known to those skilled in the art, or is used directly if already a carboxylic acid; coupling of said acid with amine yields the target product.

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## **CHART GG**

Chart GG. Isoquinoline (1) is reacted with phosphorus oxychloride or phosphorus oxybromide at temperatures ranging from room temperature to about 150 °C to yield halo-isoquinoline (2). Halo-isoquinoline (2) is reacted with an amine at temperatures ranging from room temperature to 200 °C to yield amino-isoquinoline (3). This reaction may be carried out in the presence of an organic solvent such as THF, acetonitrile, DMF, or NMP. Alternatively, the amine can be used as solvent, and a sealed reaction vessel may be used to contain volatile amine at high temperatures. Amino-isoquinoline (3) is reacted with copper (I) cyanide in an organic solvent, for example DMF or NMP (N-

25 methylpyrrolidinone) at temperatures ranging from about 120 °C

to reflux, followed by hydrolysis with an aqueous acid, for example aqueous HCl, to yield isoquinoline carboxylic acid (4). Additional methods for converting amino-isoquinoline (3) to isoquinoline carboxylic acid (4) are known to those skilled in the art and include, for example, reacting (3) with carbon 5 monoxide and an alcohol in the presence of a catalyst, for example a palladium catalyst such as palladium acetate or palladium(0) tetrakis(triphenylphosphine), and an additive, for example1,1'-bis (diphenylphosphino) ferrocene or 1,3-bis 10 (diphenylphosphino) propane, in an organic solvent, example DMF or NMP, and in the presence of a base, for example a trialkylamine or aqueous sodium or potassium carbonate or sodium or potassium hydrogen carbonate, at temperatures ranging from about 50 to about 150 °C, followed by hydroysis of the ester product to isoquinoline carboxylic acid (4). 15 Isoquinoline carboxylic acid (4) is then coupled to an amine to yield the final target product.

# **CHART HH**

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# **CHART II**

Charts HH and II. Chart HH discloses the synthesis of a set of racemic  $\alpha$ -amino sulfones while Chart II discloses the synthesis of the active enantiomer. The Michael addition of a thiol to a protected dehydroalanine methyl ester yields a sulfanyl intermediate. The sulfanyl derivative is peroxidated to the corresponding sulfone according to one of the abovementioned methods. Hydrolysis of the ester and protecting group may be carried out with a strong aqueous acid, for example 6N HCl, or acetic acid, optionally at high temperature to yield the free amino acid salt. A protecting group for

example Cbz or Boc, may be added to the amine group. Standard peptide coupling to the unprotected diamine preferentially affords the product with an unreacted  $N-R_{\rm C}$  moiety which is then orthogonally protected to yield the diprotected diamine.

Selective removal of the Rn protecting group affords a free amine. This amine can be converted according one of the above-mentioned methods into amides, carbamates,.

Alternatively, it may be reacted with an isocyanate to yield a urea, or with a sulfonyl chloride to yield a sulfonamide. The removal of the Rc protecting yields the targetcompounds. Chart II is identical to chart HH with an additional isomer separation step which may be carried out chemically, enzymatically, or by chiral chromatography, yielding the single isomer acid which is transformed into the target

## **CHART JJ**

product as described above.

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#### ChartKK

Pyridine 1 is reacted with an amine 2 in an organic solvent, for example THF, at reflux or by warming to a temperature ranging from about 80 °C to about 130 °C in a sealed vessel, to yield pyridine ester 3. Pyridine ester 3 is hydrolyzed using methods known to those skilled in the art to yield chloro-acid 4. Chloro-acid 4 is coupled to amine (VIII) using methods discussed above and known to those skilled in the art to yield final product (X).

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Alternatively, ester pyridine 3 is cyanated as taught in Tet. Lett. 2000, 41, 3271 to yield nitrile ester 5. Additional methods of preparing nitrile ester 5 include but are not limited to treatment of ester pyridine 3 with copper cyanide in organic solvents, for example N-methylpyrrolidinone, DMF at temperatures ranging from about 80 °C to about 180 °C. The ester moiety of 5 is converted to acid 6 via methods known

to those skilled in the art. Acid **5** is then coupled to amine (VIII) using methods that are discussed above or known to those skilled in the art to give final product (X).

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## Chart LL

Dinitro acid 1 is esterified with an alcohol and an acid catalyst or by methods known to those skilled in the art to yield dinitro ester 2. Dinitro ester 2 is reacted with a

protected aldehyde, for example an acetal or a ketal, in an organic solvent, for example toluene, at temperatures from about 50 to 150 °C and in the presence of an acid catalyst, for example concentrated sulfuric acid or sulfosalicylic acid, yielding dinitro amine 3. Dinitro amine 3 is treated with a palladium catalyst such as palladium on carbon in an organic solvent, for example methanol, ethanol, ethyl acetate, and acetonitrile, in the presence of an acid such as formic or acetic acid to yield amino-indole 4. Amino-indole 4 is reacted with sodium nitrite and aqueous hydrochloric or sulfuric acid, 10 followed by potassium iodide, to give iodo-indole 5. Iodoindole 5 is reacted with copper cyanide in an organic solvent, for example N-methylpyrrolidinone at temperatures from about 100 to about 200 °C to yield nitrile-indole 6. Nitrile-indole 6 is then alkylated with an alkyl halide, for example propyl or 15 butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferably DMSO, at room temperature 20 to 100 °C, to yield ester indole 7.

Alternatively, amino-indole 4 may be reacted with an aqueous mineral acid and sodium nitrite, followed by neutralization with a base, for example sodium bicarbonate, and then reacted with potassium cyanide and copper cyanide to yield nitrile-indole 6. Ester indole 7 is then hydrolyzed to indole acid 8 using methods known to those skilled in the art. Indole 8 is then coupled to amine (VIII) using methods known to those skilled in the art and previously disclosed in this document.

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Alternatively, iodo indole 5 is reacted with an alkyl halide, for example as propyl or butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, more preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO,

preferrably DMSO, at a temperature from room temperature to about 100 °C, to yield iodo alkyl 9. An Oxazole or a thiazole in an organic solvent, for example dialkyl ether or THF, at a temperature from about 0 to about -78 °C is reacted with a base, preferably butyl lithium and optionally left stirring for from about 15 to about 60 min.Zinc chloride is then added and the mixture is allowed to warm to 0-30 °C, at which time iodo alkyl 9 is added, followed by tetrakis triphenylphosphine palladium. The mixture is then optionally left stirring at a temperature from room temperature to about 80 °C to yield oxazole/thiazole indole 10. The hydrolysis of 10 by methods known to those skilled in the art yields oxazole/thiazole acid 11. Oxazole/thiazole acid 11 is coupled to amine (VIII) using methods known to those skilled in the art.

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Indole acid 1 is converted to indole ester 2 by methods known to those skilled in the art. Indole ester 2 is then alkylated with an alkyl halide, for example propyl or butyl iodide, bromide, or chloride, in the presence of a base, for

example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferrably DMSO, at room temperature to about 100 °C to yield alkyl indole 3. Alternatively, indole acid 1 may be converted directly to alkyl indole 3 by reaction with an alkyl halide, for example propyl or butyl iodide, bromide, or chloride in the presence of a base, for example sodium hydride or potassium tert-butoxide, preferably potassium tert-butoxide, in an organic solvent, for example THF, DMF or DMSO, preferrably DMSO at room temperature to about 100 °C. Alkyl indole 3 is then treated by the method disclosed in Org. Lett. (2000) 1485 and references cited therein, Tet. Lett. (1995) 4005 and references cited therein, and Org. Lett. (2001) 1005 and references cited therein to yield acylindole 4. Acylindole 4 is hydrolyzed to indole acid 5 using methods known to those skilled in the art, and indole acid 5 is coupled to amine (VIII) using methods known to those skilled in the artto yield (X).

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## BIOLOGICAL EXAMPLES

Example A
Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human

brain tissue as described in Sinha et.al, 1999, Nature 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, 10 incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further In the incubation with streptavidin/alkaline phosphatase. assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal 15 fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 20 751 mutation site.

## Specific Assay Procedure:

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Compounds are diluted in a 1:1 dilution series to a sixpoint concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-

bottom plate to which 30 microliters of ice-cold enzyme-35

substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well is transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hours incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal ( $IC_{50}$ ) compared to the enzyme reaction signal in the control wells with no added compound. In this assay, the compounds of the invention exhibited an  $IC_{50}$  of less than or equal to 20 micromolar.

## Example B

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#### 25 Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by betasecretase and having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

Biotin-SEVNL-DAEFR[oregon green]KK

Biotin-SEVKM-DAEFR[oregon green]KK [SEQ ID NO: 2]
Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK [SEQ ID NO: 3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF[oregon green]KK [SEQ ID NO: 4]

5 Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKA[oregon green]KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 -100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees C for 30 minutes. reaction is initiated by addition of 150 millimolar substrate 10 to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 15 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acqurest (Ex485 nm/ Em530 nm). The activity of 20 the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP 25 substrate. In this assay, compounds of the invention exhibited an IC50 of less than 20 micromolar.

#### Example C

## 30 Beta-secretase inhibition: P26-P4'SW assay

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in

The P26-P4'SW published PCT application W000/47618. substrate is a peptide of the sequence: [SEQ ID NO: 6] (biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF The P26-P1 standard has the sequence:

(biotin) CGGADRGLTTRPGSGLTNIKTEEISEVNL

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[SEQ ID NO: 7]

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), 30 the samples are incubated with strepavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with

streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

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#### Example D

## Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the 10 known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chouromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage 15 products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art. By way of example, one such peptide has the sequence SEVNL-[SEQ ID NO: 8], and the cleavage site is between 20 residues 5 and 6. Another preferred substrate has the [SEQ ID NO: 9], and sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the

presence of beta-secretase under conditions sufficient to

Comparison of the cleavage results in the presence of the

result in beta-secretase mediated cleavage of the substrate.

compound inhibitor to control results provides a measure of

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# Example E

## Inhibition of beta-secretase activity - cellular assay

the compound's inhibitory activity.

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et.al., 1992, Nature 360:672-674), as described in USPN 5,604,102.

The cells are incubated in the presence/absence of the
inhibitory compound (diluted in DMSO) at the desired
concentration, generally up to 10 micrograms/ml. At the end
of the treatment period, conditioned media is analyzed for
beta-secretase activity, for example, by analysis of cleavage
fragments. A beta can be analyzed by immunoassay, using
specific detection antibodies. The enzymatic activity is
measured in the presence and absence of the compound
inhibitors to demonstrate specific inhibition of betasecretase mediated cleavage of APP substrate.

#### 20 Example F

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#### Inhibition of Beta-Secretase in Animal Models of AD

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et.al., 1995, Nature 373:523-527 are useful to analyze in vivo suppression of A beta release in the presence of putative inhibitory

compounds. As described in USPN 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor preferably formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or 10 multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage 15 peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for 20 necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

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#### Example G

## Inhibition of A beta production in human patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

#### 10 Example H

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## Prevention of A beta production in patients at risk for AD

Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor preferably formulated in a carrier suitable for the chosen mode of administration.

Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereby and should only be construed by interpretation of the scope of the appended claims.

The following compounds were prepared using the above described methodology.

			Mass
Example	Structure	Compound Name(s)	Spec
	Sciucture		+H <sup>+</sup>
3552	F N N N N N N N N N N N N N N N N N N N	N'-[(1S,2S)-3- (benzylamino)-1-(3,5- difluorobenzyl)-2- hydroxypropyl]-5- methyl-N,N- dipropylisophthalamid	552.2
3553	HO N H H	N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-ethynyl-N,N-dipropylisophthalamide	590.3
3554		N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-({3-[(1E)-prop-1-en-1-yl]benzyl}amino)propyl]-5-methyl-N,N-dipropylisophthalamide	592.3
3555		N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-5-(1,3-oxazol-2-yl)-N,N-dipropylisophthalamide	647.2
3556		methyl (3-{[((2R,3S)-4-(3,5-difluorophenyl)-3-{[3-[(dipropylamino)carbonyl]-5-(1,3-oxazol-2-yl)benzoyl]amino}-2-hydroxybutyl)amino]methyl}phenyl)methylcarbamate	692.2

N'-[(1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(3-(3-(methylsulfonyl)amin olbenzyl)aminolbenzyl)aminolbenzyl)-3-hydroxy-3-(3-(methylsulfonyl)aminolbenzyl)-2-hydroxy-3-(3-(3-(methylsulfonyl)aminolpropyl)-5-(1,3-oxazal-2-yl)-1)-N,N-dipropylbenzyl)aminolpropyl)-N,N-dipropylbenzyl)aminolpropyl)-N,N-dipropylpyridine-3,5-dicarboxamide    N'-((1s,2R)-1-(3,5-difluorobenzyl)-3-(3-ethylbenzyl)aminol-2-hydroxypropyl)-N,N-dipropylpyridine-3,5-dicarboxamide 1-oxide    N'-((1s,2R)-1-(3,5-difluorobenzyl)-3-(3-ethynyl-N,N-dipropylpyridine-3,5-dicarboxamide 1-oxide    N'-((1s,2R)-1-(3,5-difluorobenzyl)-3-ethynyl-N,N-dipropylpyridine-3,5-difluorobenzyl)-2-hydroxy-3-(3-ethynyl-N,N-dipropylpyridine-2,4-dicarboxamide 1-oxide    N'-((1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(3-ethynyl-N,N-dipropylpyridine-2,4-dicarboxamide 1-oxide   N'-((1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(3-ethyl-N,N-dipropylpyridine-2,4-dicarboxamide   N'-((1s,2R)-3-(((2-tert-butylpyrimidin-4-yl)methyl]aminol-1-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   enthyl-N,N-dipropylisophthalamid	T	T	,	
difluorobenzyl)-2-hydroxy-3-[(3-corrected by the correc	3557		difluorobenzyl)-2- hydroxy-3-({3- [(methylsulfonyl)amin o]benzyl}amino)propyl ]-5-(1,3-oxazol-2- yl)-N,N- dipropylisophthalamid e	
N'-{(1s,2R)-1-(3,5-difluorobenzy1)-3-((3-hydroxypropy1)-N,N-dipropylpyridine-3,5-dicarboxamide 1-oxide   N'-{(1s,2R)-1-(3,5-difluorobenzy1)-3-((3-hydroxypropy1)-5-ethyny1-N,N-dipropylpyridine-2,4-dicarboxamide   N^4-((1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropy1)-5-ethyny1-N,N-dipropylpyridine-2,4-dicarboxamide   N^4-((1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxy-3-[(3-isopropylbenzy1) amino]propyl}-6-methyl-N^2,N^2-dipropylpyridine-2,4-dicarboxamide   N'-[(1s,2R)-3-([(2-tert-butylpyrimidin-4-yl)methyl]amino)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-3-([(2-tert-butylpyrimidin-4-yl)methyl]amino)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-3-([(2-tert-butylpyrimidin-4-yl)methyl]amino)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-3-([(2-tert-butylpyrimidin-4-yl)methyl]amino)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropylisophthalamid   N'-[(1s,2R)-1-(3,5-difluorobenzy1)-2-hydroxypropylis	2550	P P P P P P P P P P P P P P P P P P P	difluorobenzyl)-2- hydroxy-3-[(3- isopropylbenzyl)amino ]propyl}-N,N- dipropylpyridine-3,5-	1
difluorobenzy1) -3- ((3-ethylbenzy1) amino] -2-hydroxypropy1}-N, N-dipropylpyridine-3, 5-dicarboxamide 1-oxide	3338	F		
3559  N'-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethynylbenzyl) amino]-2-hydroxypropyl}-5-ethynyl-N,N-dipropylisophthalamid e  N'-{(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxyp-3-[(3-isopropylbenzyl) amino]-2-hydroxy-3-[(3-isopropylbenzyl) amino]-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylpyridine-2,4-dicarboxamide  N'-[(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxyp-3-[(3-isopropylbenzyl) amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid e  N'-[(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid e		~ N N N N N N N N N N N N N N N N N N N	<pre>difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N,N- dipropylpyridine-3,5-</pre>	
difluorobenzyl)-3- [(3- ethynylbenzyl) amino]- 2-hydroxypropyl)-5- ethynyl-N,N- dipropylisophthalamid e  N <sup>4</sup> -((1s,2r)-1-(3,5- difluorobenzyl)-2- hydroxy-3-[(3- isopropylbenzyl) amino ]propyl)-6-methyl- N <sup>2</sup> ,N <sup>2</sup> - dipropylpyridine-2,4- dicarboxamide  N'-[(1s,2r)-3-([(2- tert-butylpyrimidin- 4-yl)methyl]amino)-1- (3,5-difluorobenzyl)- 2-hydroxypropyl]-5- methyl-N,N- dipropylisophthalamid e  (M+H).	3559		describeration of the contract	
3560  N <sup>4</sup> -{(1s,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-isopropylbenzyl)amino]propyl}-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide  N'-[(1s,2R)-1-(3,5-difluorobenzyl)amino]propyl}-6-methyl-N²,N²-dipropylpyridine-2,4-dicarboxamide  N'-[(1s,2R)-3-{[(2-tert-butylpyrimidin-4-yl)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamidee		P N H OH H	difluorobenzyl)-3- [(3- ethynylbenzyl)amino]- 2-hydroxypropyl}-5- ethynyl-N,N- dipropylisophthalamid	1
difluorobenzyl)-2- hydroxy-3-[(3- isopropylbenzyl)amino ]propyl}-6-methyl- N²,N²- dipropylpyridine-2,4- dicarboxamide  N'-[(1s,2R)-3-{[(2- tert-butylpyrimidin- 4-yl)methyl]amino}-1- (3,5-difluorobenzyl)- 2-hydroxypropyl]-5- methyl-N,N- dipropylisophthalamid e  (M+H).	3560		е	i
N'-[(1s,2R)-3-{[(2-tert-butylpyrimidin-4-y1)methyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	3561	The state of the s	difluorobenzyl)-2- hydroxy-3-[(3- isopropylbenzyl)amino  propyl}-6-methyl- N <sup>2</sup> ,N <sup>2</sup> - dipropylpyridine-2,4-	
tert-butylpyrimidin- 4-y1)methyl]amino}-1- (3,5-difluorobenzyl)- 2-hydroxypropyl]-5- methyl-N,N- dipropylisophthalamid e	3301	F		
3562			tert-butylpyrimidin- 4-yl)methyl]amino}-1- (3,5-difluorobenzyl)- 2-hydroxypropyl]-5- methyl-N,N- dipropylisophthalamid	610
	3562			

3563	The second secon	N'-((1S,2R)-1-(3,5-difluorobenzy1)-3- {[(2-ethylpyrimidin-4-y1)methyl]amino}-2-hydroxypropy1)-5- methyl-N,N-dipropylisophthalamide	583 605 (M+Na)
3503	,	N'-((1S,2R)-1-(3,5-	681.3
3564	NHH NH NH NH NH NH NH NH NH NH NH NH NH	difluorobenzyl)-2- hydroxy-3-{[(1S)-1- [(isobutylamino)carbo nyl]-3- (methylsulfonyl)propy l]amino)propyl)-5- methyl-N,N- dipropylisophthalamid e	
	NH OH OH	N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-hydroxy-1-phenylpropyl)amino]propyl}-5-methyl-N,N-dipropylisophthalamide	596.3
3565			
3566	O NH H OH H NH F	N'-[(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylamino)propyl]-5-methyl-N,N-dipropylisophthalamide	606.3

3567	ON NHH OH NH	N'-((1S,2S)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)-5-methyl-N,N-dipropylisophthalamide	Mass spec (CI) MH+- OMe- tetrali ne 462.2
3568	NH H H NH NH NH NH NH NH NH NH NH NH NH	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1R)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]amino}propyl)-5-methyl-N,N-dipropylisophthalamide	Mass spec (CI) MH+- OMe- tetrali ne 462.2
3569	T Z H	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1S)-2-oxo-1-methyl-2-(methylamino)ethyl]amino}propyl)-5-methyl-N,N-dipropylisophthalamide	547.4
3570	THE THE THE THE THE THE THE THE THE THE	N'-[(1S,2R)-3-{[(1S)-1-benzyl-2-oxo-2-(methylamino)ethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3571	F T T T T T T T T T T T T T T T T T T T	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -{oxo[3-(trifluoromethyl)phenyl]methyl}glycinamide	

	HO HN F	2-{[2-({(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}amino)- 2-oxoethyl]thio}-N- (5-methylisoxazol-3- yl)acetamide	
3572	N		
	H OH H N ONH	N'-((1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(1S)-1- [oxo(methylamino)meth yl]-3- (methylthio)propyl]am ino}propyl)-5-methyl- N,N- dipropylisophthalamid	
3573		е	·
3574	H OH H OH N = ON NH F	N'-((1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-{[(1R)-1-(hydroxymethyl)-2-oxo-2-(methylamino)ethyl]amino}propyl)-5-methyl-N,N-dipropylisophthalamide	,
	H OH H  N  N  N  N  N  N  N  N  N  N  N  N  N	N'-[(1S,2R)-3-({(1S)-1-[amino(oxo)methyl]-3-methylbutyl}amino)-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamid	
3575		e	
3576	H OH H O NH <sub>2</sub>	N'-[(1S,2R)-3-[(2-amino-2-oxo-1-methylethyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
_ <del></del>	<u></u>	·	

3577	P P P	tert-butyl (1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropylcarbamat e	
3578	as drawn	tert-butyl (1S,2R)-3- (cyclopropylamino)-1- (3,5-difluorobenzyl)- 2- hydroxypropylcarbamat e	
3579	as drawn	tert-butyl (15,2R)-3- [(cyclopropylmethyl)a mino]-1-(3,5- difluorobenzyl)-2- hydroxypropylcarbamat e	
3580	O O OH H O HN NH	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[2-oxo-2- (isobutylamino)-1- methylethyl]amino}pro pyl)carbamate	416.1
3581		benzyl (1S,2R)-1- benzyl-3-[(3- ethylbenzyl)amino]-2- hydroxypropylcarbamat e	
3582	F ACI	(2R,3S)-3-amino-4- (3,5-difluoropheny1)- 1-{[1-(3- ethynylphenyl)cyclopr opyl]amino}butan-2-ol hydrochloride	357.2
3583	F N H OH H O	tert-butyl [(1S,2R)-3-{[(1S)-2-(benzylamino)-2-oxo-1-methylethyl]amino}-1-(3,5-difluorobenzyl)-2-hydroxypropyl]carbamate	478.1

		<del></del>	
	H <sub>2</sub> N OH H O	N <sup>2</sup> -[(2R,3S)-3-amino- 4-(3,5- difluorophenyl)-2- hydroxybutyl]-N <sup>1</sup> - benzyl-L-alaninamide bis(trifluoroacetate) (salt)	
	CF <sub>3</sub> COOH		-
3584	CF₃COOH		1
-3585	F N N N N N S H OH H	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[1-(2- isobutyl-1,3-thiazol- 5- yl)cyclopropyl]amino}	496.2
13383	E	propyl)carbamate	
	F OH H	(2R,3S)-3-amino-4- (3,5-difluorophenyl)- 1-{[1-(2-isobutyl- 1,3-thiazol-5- yl)cyclopropyl]amino} butan-2-ol bis(trifluoroacetate) (salt)	
•	CF₃COOH		
3586	CF₃COOH		·
3587	F N N ON N H OH H	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[1-(3- isobutylisoxazol-5- yl)cyclopropyl]amino} propyl)carbamate	480.2
	F	(2R,3S)-3-amino-4-	
	H <sub>2</sub> N OH H	(3,5-difluorophenyl)- 1-{[1-(3- isobutylisoxazol-5- yl)cyclopropyl]amino} butan-2-ol bis(trifluoroacetate) (salt)	
	CF₃COOH `		
3588	CF₃COOH		

3589	H OH H N	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-3- {[(2-ethylpyrimidin- 4-yl)methyl]amino}-2- hydroxypropyl)carbama te	437.3
3590	PH2N CF3COOH  CF3COOH	(2R,3S)-3-amino-4- (3,5-difluorophenyl)- 1-{[(2- ethylpyrimidin-4- yl)methyl]amino}butan -2-ol bis(trifluoroacetate) (salt)	
3591	NH H OH HNboc	tert-butyl {(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)amino]propyl}carbamate	477.5
3592	NH OH H COD F	tert-butyl [(1s,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-(6,7,8,9- tetrahydro-5H- benzo[7]annulen-5- ylamino)propyl]carbam ate	461.2
3593	OH NHO HOO	tert-butyl {(1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-[(3- hydroxy-1- phenylpropyl)amino]pr opyl}carbamate	451.2
3594	N O H H NH DOC	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(1S)-1- [oxo(isobutylamino)me thyl]-3- (methylthio)propyl]am ino}propyl)carbamate	504.3

		tert-butyl ((1S,2R)-	536.2
	. /	1-(3,5-	
	NH	difluorobenzyl)-2-	
	о≕′"′ н	hydroxy-3-{[(1S)-1- [(isobutylamino)carbo	
	→NH Q´İH	- ·	
	NH NH	nyl]-3- (methylsulfonyl)propy	
	O.S. F H boc	l]amino}propyl)carbam	
	/ O F 1 500	ate	
		ace	
3595	Ė		
	O F F	tert-butyl {(1S,2R)-	499.1
	O-SC F	1-(3,5-	
		difluorobenzyl)-3-	
	NH H	[(2,2-dioxido-3,4-	
Ì		dihydro-1,2-	
:	Н	benzoxathiin-4-	
	n NHboc	yl)amino]-2-	
2506	· .	hydroxypropyl}carbama	
3596	<u> </u>	te	498.1
	U E A F	tert-butyl {(1S,2R)- 1-(3,5-	498.1
	HŅ-S, 'YY'	difluorobenzyl)-3-	ı
		[(2,2-dioxido-3,4-	
	NH H	dihydro-1H-2,1-	
	OH	benzothiazin-4-	
	H NHboc	y1)amino]-2-	
	150	hydroxypropyl}carbama	
3597		te	
	Ę	tert-butyl ((1S,2R)-	461.3
		1-(3,5-	
	[ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	difluorobenzyl)-3-	
İ	/ 0 /~ '\	[[1-(3-	
	1 XOUNT NOW	ethylphenyl)cycloprop	
	H OHH	yl]amino}-2-	
2500	11 01111	hydroxypropyl)carbama	
3598		te	457.0
	7	-tert-butyl ((15,2R)	457.2
		1-(3,5- difluorobenzyl)-3-	
	)	{[1-(3-	
		ethynylphenyl)cyclopr	
	\O N \N	opyl]amino}-2-	
	H ÕHH	hydroxypropyl)carbama	
3599		te	
	F	tert-butyl ((1S,2R)-	447.2
		1-(3,5-	
		difluorobenzyl)-2-	
	1 , 0 ,	hydroxy-3-{[1-(3-	
		methylphenyl)cyclopro	
1	1 / O N Y N Y	pyl]amino}propyl)carb	
3600	H ÕH H	amate	ì
		<u> </u>	<del></del>

			==0 4
i	Γ,	tert-butyl ((1S,2R)-	558.4
		1-(3,5-	
<b>!</b>	( <u> </u>	difluorobenzyl)-2-	=
İ	, 0	hydroxy-3-{[1-(3-	
		iodophenyl)cyclopropy	
}	$N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow$	l]amino}propyl)carbam	
0.504	н онн 📗	ate	
3601	: 6:: 1:		
		tert-butyl [(1S,2R)-	462.2
ļ		3-{[3-	
	F	(cyclopropylamino)ben	
	/   H	zyl]amino}-1-(3,5-	
	TOUNT NOWN	difluorobenzyl)-2-	
	l' H oh H L J ∇	hydroxypropyl]carbama	
3602	11 01111	te	
3002	F	methyl 3-({[(2R,3S)-	465.1
	l Ì	3-[(tert-	1 400.1
	<b>人人</b> - a	butoxycarbonyl)amino]	
		-4-(3,5-	
1	BOCHN OME	difluorophenyl)-2-	
		hydroxybutyl]amino}me	
3603	ŎH H	thyl)benzoate	
	ļ F	methyl $[3-({[(2R,3S)-}$	480.1
		3-[(tert-	
		butoxycarbonyl)amino]	
!		-4-(3,5-	
	1 . N O	difluorophenyl)-2-	
	BocHN N N	hydroxybutyl]amino}me	,
3604	OHH 🕢 Ö	thyl)phenyl]carbamate	
	, <b>F</b>	methyl [3-({[(2R,3S)-	494.1
		3-[(tert-	
		butoxycarbonyl)amino]	
1	f i	-4-(3,5-	1
		difluorophenyl)-2-	
	BocHN Y N Y Y		
	OH H V	hydroxybutyl]amino}me	
2605		thyl)phenyl]methylcar	
3605		bamate	
		tert-butyl [(1S,2R)-	514.1
		1-(3.,5-	÷ ,
1	l Ll	difluorobenzyl)-3-	· ·
	<b>``</b> F Q /	({3-	
	BocHN N S N	[(dimethylamino)sulfo	
1	1 6 1 0 ,	nyl]benzyl}amino)-2-	
1	OH H V	hydroxypropyl]carbama	1
3606		te	
	F	tert-butyl [(1S,2R)-	500.1
		1-(3,5-	
		difluorobenzyl)-2-	
	∫ F	hydroxy-3-({3-	}
		[(methylsulfonyl)amin	}
1	BocHN N S	o]benzyl}amino)propyl	
3607	OH H.		1
7001	<u> </u>	]carbamate	

		1 11 [/1G 0D)	420 1
	. [	tert-butyl [(1S,2R)- 3-[(3-	432.1
		cyanobenzyl)amino]-1-	
	<u> </u>	(3,5-difluorobenzyl)-	
		2-	
	BocHN N Y	hydroxypropyl]carbama	,
3608	о́н н	te	
3000	F	3-({[(2R,3S)-3-	494.1
		[(tert-	
		butoxycarbonyl)amino]	
	F	-4-(3,5-	
		difluorophenyl)-2-	
	BocHN N T T	hydroxybutyl]amino}me	
	OH H O	thyl)phenyl	
3609		dimethylcarbamate	
	F	tert-butyl [(2R,3S)-	612.3
		4-(3,5-	
	0 0 \hspace \hspace \hspace \frac{1}{F}	difluorophenyl)-3-	ľ
' '	S	({3-	
· ·	H OH Boc	[(dipropylamino)carbo	
		nyl]-5-	
		methylbenzoyl}amino)-	
		2-hydroxybutyl][3-	1
		(ethylthio)benzyl]car	
3610		bamate	
	ÕН Н	tert-butyl ((1S,2R)-	433.2
	BocHN N.	1-(3,5-	
		difluorobenzyl)-3-	
		[(1R)-2,3-dihydro-1H-	Ì
	F—	inden-1-ylamino]-2-	l .
	·   _ /	hydroxypropyl}carbama	
3611	\rac{1}{F}	te	
	ŌH H	tert-butyl {(1S,2R)-	433.2
	BocHN N	1-(3,5-	
		difluorobenzyl)-3-	
		[(1S)-2,3-dihydro-1H-	
		inden-1-ylamino]-2-	
	F-\(\)	hydroxypropyl}carbama	
3612		te	
3012	OH " OM	tert-butyl ((1S,2R)-	449.2
1	1 _ DH	1-(3,5-	127.4
	BocHN	difluorobenzyl)-2-	
		hydroxy-3-{[(1S,2R)-	
		2-hydroxy-2,3-	
	F—( )	dihydro-1H-inden-1-	
		yl]amino}propyl)carba	
3613	F	mate	
	J		****

2614	BocHN N OH	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(1R,2S)- 2-hydroxy-2,3- dihydro-1H-inden-1- yl]amino}propyl)carba mate	449.4
3614	BocHN NH	tert-butyl ((1s,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(3s)-2- oxoazepan-3- yl]amino}propyl)carba mate	428.2
3616	BocHN NH ONH	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(3R)-2- oxoazepan-3- yl]amino}propyl)carba mate	428.2
3617	BocHN PH NOO	tert-butyl [(1S,2R)- 1-(3,5- difluorobenzyl)-3- ({[(5S)-3-ethyl-2- oxo-1,3-oxazolidin-5- yl]methyl}amino)-2- hydroxypropyl]carbama te	444.2
3617	BocHN N N O	tert-butyl [(1S,2R)- 1-(3,5- difluorobenzyl)-3- ({[(5R)-3-ethyl-2- oxo-1,3-oxazolidin-5- yl]methyl}amino)-2- hydroxypropyl]carbama te	444.2
3618	BocHN BocHN F	tert-butyl ((1S,2R)- 1-(3,5- difluorobenzyl)-3- {[1-(3-ethylphenyl)- 1-methylethyl]amino}- 2- hydroxypropyl)carbama te	475.2

		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	460 0
1	о́н н	tert-butyl {(1S,2R)-	463.3
	BocHN N N	1-(3,5-	
		difluorobenzyl)-2-	
	<u> </u>	hydroxy-3-[(2-	·
		naphthylmethyl)amino]	,
	F—(\ )	propyl}carbamate	
			Ì
3620	F		·
	он н О	tert-butyl ((1S,2R)-	458.2
	BocHN N	1-(3,5-	l i
		difluorobenzyl)-2-	
	/\ H	hydroxy-3-{[2-0x0-2-	
		(isobutylamino)-1,1-	
	F—( )	dimethylethyl]amino}p	ŀ
		ropyl) carbamate	
3621	F	10py1/carbanace	
	ОН Н	tert-butyl [(1S,2R)-	423.1
	BocHN, N.	3-[(benzyloxy)amino]-	1
1	1 ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	1-(3,5-	]
	,	difluorobenzyl)-2-	
1		hydroxypropyl]carbama	
	F( )	te	
1	"(		
3622	F		
	F .	tert-butyl 4-	1 .
		[({(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	l F	[(3-	
		ethylbenzyl)amino]-2-	
	YOUND HOH HO	hydroxypropyl amino) c	i
	´ `	arbonyl]piperidine-1-	
	HO CF <sub>3</sub>	carboxylate	
3623		trifluoroacetate	
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	1 1 1	ethylbenzyl)amino]-2-	
	N N F	hydroxypropyl}-4-	
1		fluoro-1-naphthamide	
	ОН -	Traoro-1-napirenamiade	
	NH F		
1	-		
		· ·	
			1
3624	1		
		N-[(1S,2R)-1-benzyl-	
		3-(2-butyry1-1-	
		ethylhydrazino)-2-	
	1 1 9	hydroxypropyl]-2-(3-	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	methylisoxazol-5-	
	H OH HN. O	yl)acetamide	
1	J On Pin	y 1 / accountac	1
			1
			1
3625			<u> </u>

	F	<pre>N'-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2-</pre>	·
	H OH H	hydroxypropyl}-N- hexyl-N,5-	
3626	`	dimethylisophthalamid e	
	HOHH NH N	N'-{(1S,2R)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzoyl)amino]propyl}-5-methyl-N,N-	
3627	F	dipropylisophthalamid	:
3021	CH CH	e N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-1H-imidazole-	
3628	single enantiomer	2-carboxamide	
3629	single diastereomer	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3,3-dimethyl-N <sup>2</sup> ,N <sup>2</sup> -dipropylcyclopropane-1,2-dicarboxamide	·
- 3630	Single enantiomer	tert-butyl 2- [({(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}amino)carbonyl]-1-methyl-1H-imidazol-4-ylcarbamate	•
3631	NH H OH NH NH NH NH NH NH NH NH NH NH NH NH NH	N <sup>5</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,2-dimethyl-N <sup>1</sup> ,N <sup>1</sup> -dipropylpentanediamide	·

		37 (/10 0D) 1 11	
		N-{(1S,2R)-1-benzyl-	
ļ .	O CH <sub>3</sub>	2-hydroxy-3-[(2-	,
	HO N CHa	morpholin-4-	
	NH CH OH CH OH	ylethyl)amino]propyl}	
	in the state of th	-2-(4-chlorophenoxy)-	
	)	2-methylpropanamide	ļ
	<b>└</b> ^	compound with methyl	
3632	. 6	hydroperoxide (1:2)	
	F.	N-[(1S,2R)-3-	
		(benzylamino)-1-(3,5-	-
	OH V	difluorobenzyl)-2-	
		hydroxypropyl]-4-	
	HŇ ,,,,¹	fluoro-1-naphthamide	
	HN O	_	
	HN PO		
		· .	
	ľ		
3633	<u> </u>		
	CH₃	3-	
	CH <sub>3</sub>	[(dipropylamino)sulfo	
		nyl]-N-[(1S,2R)-2-	
		hydroxy-3-	
	OH OH	(isopentylamino)-1-	
	N S H	(4-	
	CH <sub>3</sub> CH <sub>3</sub> NH	isopropylbenzyl)propy	•
		1]propanamide	
2624			
3634	CH <sub>3</sub> CH <sub>3</sub>		
	CH <sub>&amp;</sub>	3-	
	l I	[(dipropylamino)sulfo	
İ		nyl]-N-[(1S,2R)-2-	
		hydroxy-3-	
	□ CH <sub>3</sub>	(isopentylamino)-1-	
	HO	(3-	
	H O'N	methoxybenzyl)propyl]	
	HŅ CH <sub>3</sub>	propanamide	
	in the state of th		ŀ·····································
		1	l
-	1 1		
3635	CH <sub>3</sub> CH <sub>3</sub>		
	CH <sub>3</sub>	$N^{1}-[(1S, 2R)-1-(3, 5-$	
1	Ĭ	dichlorobenzyl)-2-	
		hydroxy-3-	
į	CI N	(isopentylamino)propy	1
1	CH <sub>3</sub>	1]-N <sup>5</sup> , N <sup>5</sup> -	
		dipropylpentanediamid	
	CC C	e	
	HO. 3	l ~	
	I CH <sub>2</sub> Y N U		
	L L° \ J H		
1	CH <sub>3</sub> N H		
3636			

		N <sup>1</sup> -[(1S,2R)-3-	· ·
		(benzylamino)-2-	
·		hydroxy-1-(4-	
	J	methoxybenzyl)propyl]	
	HŅ	-5-methyl-N <sup>3</sup> , N <sup>3</sup> -	
	. ₩₩ <b>_ \_OH</b>	dipropylisophthalamid	
		e	
	CH <sub>3</sub>		
			.
3637	ĊH <sub>3</sub> CH <sub>3</sub> Ö		
		$N^{1}$ -[(1s,2R)-3-	
	Ų /γ CH₃	(benzylamino)-2-	
	NH O	hydroxy-1-(4-	
		methoxybenzyl)propyl]	
	HO! (	-N <sup>3</sup> , N <sup>3</sup> -	
		dipropylbenzene- 1,3,5-tricarboxamide	
	HN HN	1,3,5-cricarboxamide	
	<u>`</u> —o		,
	o. —		·
	CH₃ N		
	⟩		
3638	CH₃∕ Ő		
	CH <sub>3</sub>	$N^1 - \{ (1S, 2R) - 2 - 1 \}$	
	)	hydroxy-1-(4- isopropylbenzyl)-3-	
		[(3-	
		methoxybenzyl)amino]p	
	\	ropyl}-N <sup>3</sup> , N <sup>3</sup> -	
İ	HN OH	dipropylbenzene-	
		1,3,5-tricarboxamide	
	>\		·
	HN )		
	<b>&gt;=0</b> (/ <b>&gt;</b>	_	
	CH₃		
	N CH₃		
	NH <sub>2</sub>		
3639	CH <sub>3</sub> CH <sub>3</sub> O		
	CH ₩	3- [(dipropylamino)sulfo	
	O CH <sub>3</sub>	nyl]-N-((1S)-1-{(1R)-	
	HO N S N	1-hydroxy-2-[(3-	
	CH <sub>3</sub> H O N CH <sub>3</sub>	methoxybenzyl)amino]e	
	CH <sub>3</sub> N	thyl}but-3-	
1	1		1
3640		ynyl)propanamide	1

		<del></del>	
	<b></b> 0	N <sup>1</sup> -[(1S,2R)-1-(2-	
		furylmethyl)-2-	
·	+	hydroxy-3-	
	HO N	(isopentylamino)propy	
	H CH <sub>3</sub> CH <sub>3</sub>	1]-N <sup>5</sup> , N <sup>5</sup> -	
	HŅ Ong Ong	dipropylpentanediamid	
		e e	
3641	CH₃ CH₃		
7041	CH <sub>3</sub>	N1 (/10 0P) 1 /0	
		N <sup>1</sup> -[(1S,2R)-1-(2-	
	CH <sub>3</sub>	furylmethyl)-2-	
	5.13	hydroxy-3-	
	NH	(isopentylamino)propy	
	_ \OH _	$1]-5-methyl-N^3,N^3-$	ľ
		dipropylisophthalamid	
	CH <sub>3</sub> L.J., L.	e	
	l T		
	$N \sim 0$		
	1 1 1	•	
3642	ĆH₃		
	ÇH₃	N <sup>1</sup> -[(1S,2R)-2-	
	ا 🔈 ا	hydroxy-3-[(3-	,
		methoxybenzyl)amino]-	
		1-(1-	
		naphthylmethyl)propyl	
	HN /	$]-5-methyl-N^3, N^3-$	
	OH	dipropylisophthalamid	·
		e	
		·	
	$N \sim 0$		
2542	CH <sub>3</sub> CH <sub>3</sub>		
3643	, · · · ·		
	CH₃	$N^{1}-((1S)-1-\{(1R)-1-$	
	) 	hydroxy-2-[(3-	
-	· /=<	methoxybenzyl)amino]e	
		thyl}-3-methylbutyl)-	
	<u> </u>	N <sup>3</sup> , N <sup>3</sup> -dipropylbenzene-	
1	' ` ` <b>`</b> ` `	1,3,5-tricarboxamide	
	HN OHCH3		
[	CH <sub>3</sub>	·	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		
	HN		
	)=o		
1			
1			
1			
12644	NH <sub>2</sub>		
3644	`сн <sub>3</sub> с <sub>Н3</sub> о́		

	CH₃ [	$N^{1}-[(1S,2R)-1-(2-$	•
		furylmethyl)-2-	
	CH3 —NH OH ( )	hydroxy-3-	
	<u> </u>	(isopentylamino)propy	
	>/	$1]-N^3, N^3-$	İ
	HNÍ I	dipropylbenzene-	
}	<u></u>	1,3,5-tricarboxamide	
,	0. ∕≕	•	ľ
	<b>)</b>		•
	N		Ì
	⟨	}	
3645	CH₃ CH₃ Ő ¯		1
3043	CH <sub>3</sub>	$N^{1}-[(1S,2R)-2-$	
	0	hydroxy-3-[(3-	
		methoxybenzyl)amino]-	
	<u>/</u> _\	1-(1-	
		naphthylmethyl)propyl	
		$]-N^3,N^3-$	
		dipropylbenzene-	
j i	HN OH	1,3,5-tricarboxamide	
		1,5,5-CIICAIDOXAMIDE	
	?'''' <b></b>		
	HN		
	<b>)=</b> 0		
	Q /=<		
	N		
	\ \ \\ \\_\NH <sub>2</sub>		
3646	CH₃ CH₃ O		
		N-{(1S,2R)-1-benzyl-	
		2-hydroxy-3-[(3-	
ľ	O CH <sub>3</sub>	methoxybenzyl)amino]p	
	HO N S	ropy1}-3-{[(2-	
ļ	HCI HON	methoxyethyl)(propyl)	
	HCI NH	amino]sulfonyl}propan	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	amide hydrochloride	
	CH <sub>3</sub>	_	
1	<b> </b>		
3647	O <sub>CH3</sub>		
		N-{(1S,2R)-1-benzyl-	
		2-hydroxy-3-[(3-	
		methoxybenzyl)aminolp	
	O	ropy1}-3-(4,5-	1
1		dimethyl-2-furoyl)-5-	
		methylbenzamide	
	HŅ HŅ		
	CH <sub>3</sub> CH <sub>3</sub>		1
			•
	1		
	O_CH <sub>3</sub>		
3648	Ĭ		
		<u> </u>	

OU.	3	
CH <sub>3</sub> N CH <sub>3</sub>	[(dipropylamino)sulfo nyl]-N-[(1S,2R)-2- hydroxy-3- (isopentylamino)-1-	
CH <sub>3</sub> CH <sub>3</sub>	(4- methylbenzyl)propyl]p ropanamide	
HO HO CH	1 3- [(dipropylamino) sulfo nyl]-N-{(1S,2R)-1-(3- fluoro-5- hydroxybenzyl)-2- hydroxy-3-[(3- methoxybenzyl) amino]p ropyl}propanamide	
U^CH₃		
HN OH F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-1,3-benzothiazole-2-carboxamide	
F		
F HO CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-iodobenzyl)amino]propyl}-5-(2,5-dimethylphenoxy)-2,2-dimethylpentanamide	
		<u> </u>
HO HO CH <sub>3</sub>	N-[(1S,2R)-3-amino-1- (3,5-difluorobenzyl)- 2-hydroxypropyl]-3- (isopentylsulfonyl)pr opanamide trifluoroacetate	
CH <sub>3</sub> OH F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-2-hydroxy-5-methylbenzamide	471.4
		[(dipropylamino) sulfo nyl]-N-[(1s, 2R)-2-hydroxy-3-(isopentylamino)-1-(4-methylbenzyl) propyl]p ropanamide  1 3-[(dipropylamino) sulfo nyl]-N-((1s, 2R)-1-(3-fluoro-5-hydroxy-3-[(3-methoxybenzyl)-2-hydroxy-3-[(3-methoxybenzyl)-2-hydroxy-3-[(3-iodbenzyl) amino]prop yl)-1,3-benzothiazole-2-carboxamide  N-((1s, 2R)-1-(3, 5-difluorobenzyl)-2-hydroxy-3-[(3-iodbenzyl)-3-[(3-iodbenzyl)-3-[(3-iodbenzyl)-3-[(3-iodbenzyl)-3-[(3-iodbenzyl)-3-[(3-iodbenzyl)-3-[

	HO NH2 F OH F OH	4-amino-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}butanam	
3655	CH <sub>3</sub>	ide bis(trifluoroacetate)	
3656	S CH <sub>3</sub>	N-{(1s,2k)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(pyridin-4-ylmethyl)thio]benzamide	
3030	N <sub>O</sub>	N-{(1S,2R)-1-(3,5-	
3657	F HO NH CH <sub>3</sub>	difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2,1,3- benzoxadiazole-5- carboxamide	)
	F HO CH <sub>3</sub>	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-methyl-1,2,3-thiadiazole-5-carboxamide	
3658	- · · · · · · · CH <sub>3</sub> · · · ·		
3659	CH <sub>3</sub> HN HN HN N OH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-[(pyridin-2-ylthio)methyl]-2-furamide	

			<del></del>
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	CH₃	[(3-	
	N	ethylbenzyl)amino]-2-	
	CH <sub>3</sub> N O	hydroxypropyl}-1-	
		phenyl-5-propyl-1H-	
	HN F	pyrazole-4-	
		carboxamide	
	NOH Y		
3660	O., [		
3000	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
	J. 13	difluorobenzyl)-3-	
		[(3-	
	HN-	ethylbenzyl)amino]-2-	
	н >ОН .F	hydroxypropyl}-5-	
1	N HN	(trifluoromethoxy)-	l
		1H-indole-2-	
		carboxamide	1
1	Ŭ_F · F		
3661	F <sup>/</sup> F		
	F	N-{(1S,2R)-1-(3,5-	•
		difluorobenzyl)-3-	
		[(3-	
	0	ethylbenzyl)amino]-2-	•
	→ J.J. VOH	hydroxypropyl}-4-(5-	
	CH <sup>a</sup> L X N J	methyl-1H-tetraazol-	•
		1-yl)benzamide	
	N HŅ		
	N=N CH <sub>3</sub>		
	CH3	· ·	
3662			
	ÇH₃	N-{(1s,2R)-1-(3,5-	
	CH <sub>3</sub> N	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
	F NH	hydroxypropy1)-2,8-	
	H L CH <sub>3</sub>	dimethylquinoline-3-	
	HO N	carboxamide	
3663			
	F	2-(3-chlorophenoxy)-	
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	F O	[(3-	
	HO₄ Ž, Č CH₃	ethylbenzyl)amino]-2-	
	HO N CH <sub>3</sub>	hydroxypropyl}propana	
Ì	LH b	mide	
	NH NH		
	\		
3664	`CH₃		

			<del></del>
		2-chloro-N-{(1s,2R)- 1-(3,5- difluorobenzyl)-3- [(3-	
	CI O F N \OH \F	ethylbenzyl)amino]-2- hydroxypropyl}-4-(1H- tetraazol-1- yl)benzamide	
3665	N=N CH <sub>3</sub>		
	CH <sub>3</sub> N N N OH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[5-(2-methylphenyl)-2H-tetraazol-2-yl]acetamide	
3666	F O O S N	3-(1,3-benzoxazol-2-ylthio)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}propanamide	
3667	CH <sub>3</sub>		·
	HO N CH <sub>3</sub> OH CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3[(3ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-6-methylquinoline-4-carboxamide	
3668	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-	
3669	N+ CH <sub>3</sub> F	propylpyrazine-2- carboxamide 4-oxide	

	T		
	ÇH₃	N-{(1S,2R)-1-(3,5-	
	<b>\</b>	difluorobenzyl)-3-	
		[(3-	
	( )	= ·	
	S L	ethylbenzyl)amino]-2-	
İ		hydroxypropyl}-1-	
		benzothiophene-3-	
1	NH HN	carboxamide	
,	/ NH )		
	, <u>, , , , , , , , , , , , , , , , , , </u>		
	) OH		
	↓ On		
	\_ <i>&gt;</i> _F		
3670			
30.0	<u></u>		
	CH₃	N-{(1S,2R)-1-(3,5-	
	· /	difluorobenzyl)-3-	į
	CH₃ ∕	[(3-	i
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-1-	
		methyl-1H-indole-3-	
	\HN		
	_∕_NH'"\	carboxamide	
	0 \ \	į	
	S' 7	1 .	
	\ Он		i
		•	·
	\ \\_ <sub>E</sub>		
2671			
3671	<u> </u>		
1	CH <sub>3</sub> (	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	·	[(3-	
	HN−√	ethylbenzyl)amino]-2-	
	> <del>-</del> OH F	hydroxypropyl}-6-	,
	N HN		
		methoxy-1,3-	
		benzothiazole-2-	
		carboxamide	ŀ
3672	ĊH <sub>3</sub> F		
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	l
"	· · · · · · · · · · · · · · · · · · ·	F (3 - · · · · · · · · · · · · · · · · · ·	-
		ethylbenzyl)amino]-2-	
	HN.	hydroxypropyl}-2-[(6-	
		methoxy-1H-	
	Ung N L	benzimidazol-2-	
	N S N OH	yl)thio]acetamide	
	Ö ¬	, -,,	· ·
	1 7		
3673	Ļ		
	<u></u>	<u></u>	

	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-	
3674	HN	phenylthiophene-2- carboxamide	
	CH <sub>3</sub> HN OH F OS O	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methoxythiophene-2-carboxamide	
3675	CH <sub>3</sub> F	27 (// 2 2 2 2 4 7 2 5	
		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-	
3676	F HO NH CH <sub>3</sub>	ethylbenzyl)amino]-2- hydroxypropyl}-2,3'- bithiophene-5- carboxamide	,
	F HO N H NH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-morpholin-4-yl-4-oxobutanamide	
3677	CH <sub>3</sub>		
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-indole-3-carboxamide	
3678	OH F		

	Е	4-(acetylamino)-N-	
	<u> </u>	{ (1S, 2R) -1-(3,5-	
		difluorobenzyl)-3-	
	ÇH₃ Q	[(3-	
	, J., OH	ethylbenzyl)amino]-2-	
	O L A N J.	hydroxypropyl}-2,6-	
	CH <sub>3</sub> N CH <sub>3</sub> HŅ	dimethylbenzamide	
	H		
	CH <sub>3</sub>		
3679			
	CH <sub>3</sub>	N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	
	HN O	furamide	
Į.	NH NH		
	HO, NH		
	F		
3680	F	N-{(1S,2R)-1-(3,5-	
	HO/,	difluorobenzyl)-3-	
	רוד או זי ריון ו	[(3-	
ļ	F NH	ethylbenzyl)amino]-2-	
		hydroxypropyl}-4-	
	CH <sub>3</sub> CH <sub>3</sub>	hydroxy-3,5-	
:	но	dimethoxybenzamide	
	i I		
3681	O <sub>CH3</sub>	4 200ty/ N (/10 2P)	
		4-acetyl-N-{(1S,2R)- 1-(3,5-	
		difluorobenzyl)-3-	
-		[(3-	
	F , OH	ethylbenzyl)aminol-2-	
		hydroxypropyl)benzami	
	CH <sub>3</sub> H <sub>N</sub>	de	
	CH <sub>3</sub>		
3682			

		77 ( (1 G 2 D ) 1 /2 E	<del></del>
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-	1
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}nicotin	
	N: LINI	amide	
	N HN .		
	OH OH		
	0 - F		
3683	Ė		
	ÇH₃	N-{(1S,2R)-1-(3,5-	
	N OH	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	ļ
	ONH HN	hydroxyquinoline-4- carboxamide	
	'''\	Calboxanitae	
1.	ЬOH		
			,
3684	F F		
3004	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-	
	J 3	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-6-	
	HO HN	hydroxynicotinamide	
	N N OH		
3685	<u> </u>		
3003	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	HN-\	ethylbenzyl)amino]-2-	
	)—OH ,F	hydroxypropyl}-1-	
	s HN-	benzothiophene-2-	
Ì		carboxamide	
3686			
3000	N Cl	7-chloro-N-{(1S,2R)-	
		1-(3,5-	1
		difluorobenzyl)-3-	,
	F. NH OH	[(3-	
		ethylbenzyl)amino]-2-	
	HO N CH <sub>3</sub>	hydroxypropyl}-4-	
	···	hydroxyquinoline-3-	
3687	<u>'</u>	carboxamide	<u> </u>

Т	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-	
	)	difluorobenzyl)-3-	
	$\sim$	[(3-	
	CH <sub>3</sub> N	ethylbenzyl)amino]-2-	
		hydroxypropyl}-3- methylisoxazole-5-	
ļ	HN	carboxamide	
	NH HN	Carbonamia	
	,ı.\ <u>\</u>		
	\ о́н		
3688	F	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
· ·	F .	ethylbenzyl)amino]-2-	
	HO I	hydroxypropyl}-5-	,
	N N N	methylisoxazole-3- carboxamide	
	NH O	Carboxamic	
	CH₃		
3689	CH <sub>3</sub>		
	1	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
	, VOH	hydroxypropyl}-4-	
	N H	(3,5-dimethyl-1H-	
	I INSM	pyrazol-1-   yl)benzamide	<u> </u>
		Ja, Jonauma de	
	CH <sub>3</sub>	·	
2600	CH₃		
3690	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
	5.13	difluorobenzyl)-3-	
		[(3-	,
	HN—OH F	ethylbenzyl)amino]-2-	
	H HN	hydroxypropyl}-5- methoxy-1H-indole-2-	1
		carboxamide	
	0 0		
3691	O F		

	•		
	H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,5-dimethyl-3-furamide	•
3692	<u> </u>		
	N H HO NH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-6-hydroxy-2-(methylthio)pyrimidine-4-carboxamide	
3693			•
-	HQ. HN	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-1,3-oxazole-4-	
	HN	carboxamide	
3694	F	N (/10 2P) 1 /2 F	
	HO HN	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3methyl-1H-pyrazole-5-carboxamide	
3695	H HN N'N		

		N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-	
		[(3-	
	110	ethylbenzyl)amino]-2-	
	HO HN	hydroxypropyl}thiophe ne-3-carboxamide	
	[	110 0 0022011011200	
	HN		
	F		
13696	· F	6-chloro-N-{(1S,2R)-	
	CI ·	1-(3,5-	
		difluorobenzyl)-3-	
		[(3- ethylbenzyl)amino]-2-	
	HŃ	hydroxypropyl}-1H-	
	NH ONH	indole-2-carboxamide	٠,
	OH		
	F		. 1
	NH \		
3697		N-{(1S,2R)-1-(3,5-	
	H	difluorobenzyl)-3-	
	N H OHH	[(3-	
	N N N N N N N N N N N N N N N N N N N	ethylbenzyl)amino]-2- hydroxypropyl}-1H-	
	Ö 🆴 F	indole-5-carboxamide	·
3698			
	./О Н ОН Н	N-{(1S,2R)-1-(3,5-	
	N N N	difluorobenzyl)-3-	
	<i>l</i>	ethylbenzyl-)amino]-2-	
		hydroxypropyl}-4- methyl-1,3-oxazole-5-	
3699	ļ F	carboxamide	
	0	N-{(1S,2R)-1-(3,5-	,
	H N A F	difluorobenzyl)-3-	
		ethylbenzyl)amino]-2-	
	OH	hydroxypropyl}-4-	
	NH F	methoxybenzamide	
3700			

N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-piperidin-1-ylbenzamide	
	**
3702	
N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methylpyrimidine-5-carboxamide	
3703	
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropyl}quinoline-4-carboxamide	

i	F, N	N-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(3-	
		ethylbenzyl)amino]-2-	
	NH \	hydroxypropyl}-2-	
	F HO⊷	phenylimidazo[1,2-	
	NH —	a]pyridine-7- carboxamide	
		Carboxamide	
3705	CH <sub>3</sub>		
	CH <sub>3</sub> \	N-{(1s,2r)-1-(3,5-	
		difluorobenzyl)-3-	
	HN—	ethylbenzyl)amino]-2-	
	CH₃ →OH F	hydroxypropyl}-6-	
	HN-	hydroxy-4-	
	N N	methylpyridine-2- carboxamide	
3706	но ғ		
		N <sup>1</sup> -{(1s,2R)-1-(3,5-	,
		difluorobenzyl)-3-	
	CH <sub>3</sub>	ethylbenzyl)amino]-2-	'
		hydroxypropy1}-N4,N4-	
	F NH	diphenylsuccinamide	
		i i	-
3707	HO		
3707	Ę	N-{(1S,2R)-1-(3,5-	
į.	<b>)</b>	difluorobenzyl)-3-	
	OH ()—F	[(3-	
	NH	ethylbenzyl)amino]-2- hydroxypropyl}-2-	
	HN HN	[ethyl(methyl)amino]-	,
	{	4-hydroxypyrimidine-	
	CH₃	5-carboxamide	
	N N		
-			
3708	CH₃ CH₃		
	F	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
1	F O OH	ethylbenzyl)amino]-2-	•
	HO N.	hydroxypropyl}-4,8-	
		dihydroxyquinoline-2-	
	H NH	carboxamide	
	OH OH		
3709	CH₃	·	
	<u> </u>		

	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	HN	[(3- ethylbenzyl)amino]-2-	
	→OH ,F	hydroxypropyl}-1-	
	Q HN	benzofuran-2-	
		carboxamide	
3710	F		
	CH₃	N-{(1s,2r)-1-(3,5-	-
		<pre>difluorobenzy1)-3- [(3-</pre>	1
		ethylbenzyl)amino]-2-	
	<b>)</b>	hydroxypropyl}-1-	
	<u>,                                    </u>	ethyl-1H-indole-2-	
	CH₃ HÌN— → OH F	carboxamide	
	N HN		
3711	) V		
3/11	Ę Ę	2-(acetylamino)-N-	·
	F	{(1s,2R)-1-(3,5-	:
	OH C	difluorobenzyl)-3-	
		[(3- ethylbenzyl)amino]-2-	
	NH HN.	hydroxypropyl}-4,5-	
	) 0	dimethylthiophene-3-	
	CH <sub>3</sub>	carboxamide	
	CH <sub>3</sub> CH <sub>3</sub> S CH <sub>3</sub>	·	
3712	CH <sub>3</sub> CH <sub>3</sub> S —CH <sub>3</sub>		
	F	N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		ethylbenzyl)amino]-2-	·
•	F 0	hydroxypropyl}-3-	
	HONN	hydroxyquinoxaline-2-	
	NH HO N	carboxamide	
3713	CH <sub>3</sub>		
3/13		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	OH DH	[(3- ethylbenzyl)amino]-2-	
	~NH \····	hydroxypropyl}-1H-	
	/—  HN	indazole-3-	
-	<b>&gt;</b> 0	carboxamide	
	ĆH₃ N=	·	
	HN		
3714			

	CH <sup>3</sup>	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3-	
[	NH NH	ethylbenzyl)amino]-2-	
	", "H — au	hydroxypropyl}-5-	
1	HO N CH <sub>3</sub>	methyl-2-phenyl-1,3- oxazole-4-carboxamide	
3715	<u> </u>	4-chloro-N-{(1S,2R)-	
		1-(3,5-	
		difluorobenzyl)-3-	
	F Q	[(3-  ethylbenzyl)amino]-2-	
	HONN	hydroxypropyl}-6-	
	H CH3	methylquinoline-2-	
,	NH CH₃	carboxamide	
	CH <sub>3</sub>		,
3716			
	CH <sub>3</sub> CH <sub>8</sub> /=	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-	
		[(3-	
	NHO"	ethylbenzyl)amino]-2-	
	HN—	hydroxypropyl}-N <sup>2</sup> ,N <sup>2</sup> -dimethylphthalamide	
	но У	dimodify apronduction	
		·	
			,
3717	F	1 (4 7 07) 4 (2 7	
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-	
		[(3-	
	HN-OH F	ethylbenzyl)amino]-2- hydroxypropyl}thiophe	
	HN OH F	nydroxypropy1}thTophe ne-2-carboxamide	
1,			
3718	F F		
	F	N-{(1S,2R)-1-(3,5-	
}		difluorobenzyl)-3-	
	F O	ethylbenzyl)amino]-2-	
	HO. T.	hydroxypropyl}-3- furamide	
	H L	Tutamirae	
	NH _O		,
1			
		·	
3719	CH₃	<u> </u>	L

_			,
	F O CH <sub>3</sub>	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-methyl-3-furamide	
3720	CH <sub>3</sub>		
3721	CH <sub>3</sub> HN  OH  HN  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-6-neopentylpyridine-2-carboxamide	
3722	F HO NH CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1,3-thiazole-4-carboxamide	
3723	CH <sub>3</sub> S O NH OH H CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzothiophene-5-carboxamide	
3724	CH <sub>3</sub> CH <sub>3</sub> F  NH OH  H  CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-hydroxy-7-methoxy-1-benzofuran-5-carboxamide	

N-((1s,2R)-1-(3,5-difluorobenzyl)-3-		<del>,</del>		
[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenyl-1,3-oxazole-4-carboxamide				
## stylenzyl amino] -2- hydroxypropyl) -2- hydroxypropyl) -2- hydroxypropyl) -2- hydroxypropyl) -3- carboxamide  N-{(1s, 2R) -1-(3, 5- difluorobenzyl) amino] -2- hydroxypropyl) -3, 4- dihydroxypropyl) -3, 4- dihydroxypropyl) -3, 4- dihydroxypropyl) -N'- phenylsuccinamide     NI-((1s, 2R) -1-(3, 5- difluorobenzyl) -N'- phenylsuccinamide    NI-((1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N'- phenylsuccinamide    NI-((1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N'- pyridin-3- ylsuccinamide			difluorobenzyl)-3-	
## stylenzyl amino] -2- hydroxypropyl) -2- phenyl -1, 3-oxazole -4- carboxamide  N-{(1s, 2R) -1-(3, 5- difluorobenzyl) -3, 4- dihydroxypropyl) -3, 4- dihydroxypropyl) -3, 4- dihydroxypropyl) -N- phenylsuccinamide  N-{(1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N- phenylsuccinamide  N-{(1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N- phenylsuccinamide  N-{(1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N- phenylsuccinamide	<u>'</u>		[ (3-	ļ
hydroxypropyl}-2-   phenyl-1,3-oxazole-4-   carboxamide	<b>\</b>	E A // NH A		
3725    HO   N   OH   Carboxamide   N   (1s, 2r) -1 - (3, 5 - difluorobenzyl) -3, 4 - dihydroxybenzamide				ì
3725  F  CH <sub>8</sub> HN  CH <sub>8</sub> HN  OH  HN  OH  HN  OH  HN  OH  HN  OH  HN  OH  F  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(3-ethylbenzyl) amino]-2-hydroxypropyl)-3,4-dihydroxybenzamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(3-ethylbenzyl) amino]-2-hydroxypropyl)-N-hydro		し		
N-{(15,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-3,4-dihydroxybenzamide  N^-((15,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-N^-phenylsuccinamide  N^-((15,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-N^-phenylsuccinamide  N^-((15,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-N^-pyridin-3-ylsuccinamide		HO, A HO,		
difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-3,4- dihydroxybenzamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-M'- phenylsuccinamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-N'- phenylsuccinamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-N'- pyridin-3- ylsuccinamide	3725	ļ ģ	carboxamide	•
difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-3,4- dihydroxybenzamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-M'- phenylsuccinamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-N'- phenylsuccinamide  N <sup>1</sup> -{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-N'- pyridin-3- ylsuccinamide		F	N-{(1S,2R)-1-(3,5-	
3726  CH <sub>3</sub> H  H  H  O		Ou l		1
are thylbenzyl) amino] -2- hydroxypropyl} -3, 4- dihydroxybenzamide  Nt-{(1s, 2r) -1-(3, 5- difluorobenzyl) amino] -2- hydroxypropyl} -N4- phenylsuccinamide  Nt-{(1s, 2r) -1-(3, 5- difluorobenzyl) -N4- phenylsuccinamide  Nt-{(1s, 2r) -1-(3, 5- difluorobenzyl) -N4- phenylsuccinamide  Nt-{(1s, 2r) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl} -N4- pyridin-3- ylsuccinamide		CH <sub>2</sub> N On		
are thylbenzyl) aminol -2-hydroxypropyl}-3,4-dihydroxybenzamide  N1-{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-N4-phenylsuccinamide  N1-{(15,2R)-1-(3,5-difluorobenzyl)-N4-phenylsuccinamide}  N1-{(15,2R)-1-(3,5-difluorobenzyl)-N4-phenylsuccinamide}		H		
hydroxypropyl)-3,4- dihydroxybenzamide  N1-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-N4- phenylsuccinamide  N1-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-N4- pyridin-3- ylsuccinamide				
3727  NH  NH  NH  NH  NH  NH  NH  NH  NH  N		]":	hydroxypropyl}-3,4-	
3727  NH  NH  NH  NH  NH  NH  NH  NH  NH  N			dihydroxybenzamide	
3727  NH  H  OH  NI-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1]-N4-phenylsuccinamide  NI-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1]-N4-pyridin-3-ylsuccinamide	1			
3727  NH  H  OH  NI-((1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-N4-phenylsuccinamide  NI-((1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1)-N4-pyridin-3-ylsuccinamide	1	но 📉		· ]
NH  NH  NH  NH  NH  NH  NH  NH  NH  NH	2726			
difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl}-N'- phenylsuccinamide  NH  NH  NH  NH  NH  NH  NH  NH  NH  N	3/20	<u> </u>	xt (/10 2p) 1 /2 f	
NH  NH  NH  NH  NH  NH  NH  NH  NH  NH				
ST27  OHF  ethylbenzyl) amino]-2- hydroxypropyl}-N^4- phenyl succinamide  NH  H  OHF  NH  NH  NH  NH  NH  NH  NH  F  NH  NH	1	1 6 4		
3727  NH  NH  NH  NH  NH  NH  NH  NH  NH  N		NH L		
hydroxypropyl}-N <sup>4</sup> -phenylsuccinamide  NH  NH  NH  NH  NH  NH  NH  NH  NH  N	•		ethylbenzyl)amino]-2-	
phenylsuccinamide  NH  CH <sub>3</sub> N <sup>1</sup> -{(1s, 2R)-1-(3, 5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -pyridin-3-ylsuccinamide	]·			
NH  NH  NH  NH  NH  NH  NH  NH  NH  NH	}			
3727  NH  NH  NH  NH  NH  NH  NH  NH  NH  N		//OH/	phenyisuccinamice	1 '
NH H H NH F NH F NH F NH F NH F NH F NH	İ	NIL E		·
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NH H H NH F NH F NH F NH F NH F NH F NH	1	1		
NH H H NH F NH F NH F NH F NH F NH F NH				
NH H H NH F NH F NH F NH F NH F NH F NH	ļ			
NH H H NH F NH F NH F NH F NH F NH F NH				
NH H H NH F NH F NH F NH F NH F NH F NH		, Lu		
NH H NH F NH F (15,2R)-1-(3,5-difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>4</sup> -pyridin-3-ylsuccinamide	1	CH3		
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>4</sup> - pyridin-3- ylsuccinamide	3727	\		
NH H H ethylbenzyl)amino]-2-hydroxypropyl}-N4-pyridin-3-ylsuccinamide			$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
NH H H ethylbenzyl)amino]-2-hydroxypropyl}-N4-pyridin-3-ylsuccinamide	1		difluorobenzyl)-3-	l
ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>4</sup> - pyridin-3- ylsuccinamide	1	N NIL		Į
hydroxypropy1}-N <sup>4</sup> - pyridin-3- ylsuccinamide	}	I INC. H		
O OH pyridin-3- ylsuccinamide	ļ	N N F		· '
NH F Ylsuccinamide	1			
NH F YISUCCINAMITUE	1	i o / aut		
NH F	1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	ylsuccinamide	
	1	NH F	<sup>-</sup>	)
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2720	1			, "
2720	}			Ì
#2720 I OU	1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	<b>,</b>	
3728 CH3	3728	CH <sub>3</sub>		

	011	vi (40 00) 4 (2 5	
	CH <sub>3</sub>	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 4) \}$	
	<u></u>	difluorobenzyl)-3- [(3-	
	<b>↑ `NH</b> H _	ethylbenzyl)amino]-2-	
	CH <sub>3</sub> N	hydroxypropyl}-N <sup>4</sup> -	
		(2,6-	
	O C''OH	dimethylphenyl)succin	
	NH F	amide	i
		·	
-			
	<b>.</b>		
3729	ĊН <sub>3</sub>		
	CH <sub>3</sub>	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
1		difluorobenzyl)-3-	
		[(3-	
	L, CH <sub>3</sub>	ethylbenzyl)amino]-2-	
	l 🍑 ]   N J	hydroxypropyl}-N4-	
	HN O H	methylsuccinamide	
	HO, NH		
	F. A.		: .
3730	<u> </u>		
	F	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	CH <sub>3</sub>	[(3-	
	F 0	ethylbenzyl)amino]-2-	i
	HO <sub>s</sub> il \ \ \	hydroxypropyl}-3-(4-	
	H O	methoxyphenoxy)propan	
•	NH	amide	
			•
	<b>)</b>		
2721	<u></u>		·
3731	°CH₃	N (/10 0D) 1 /2 5	
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-4-	
]	F NH OH	hydroxy-7-	
	HO N CH <sub>3</sub>	methoxyquinoline-3-	
3732	i ii ii ii ii ii ii ii ii ii ii ii ii i	carboxamide	, '
	F	N-{(1S,2R)-1-(3,5-	
	ai A OH	difluorobenzyl)-3-	
	CH <sub>3</sub> N	[(3-	'
		[ ] [	
		ethylbenzyl)amino]-2-	
	HN HN	ethylbenzyl)amino]-2- hydroxypropyl}-4-	·
	HN	ethylbenzyl)amino]-2- hydroxypropyl}-4- [methyl(methylsulfony	
		ethylbenzyl)amino]-2- hydroxypropyl}-4-	·
3733·	HN	ethylbenzyl)amino]-2- hydroxypropyl}-4- [methyl(methylsulfony	

	HN O O OH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-	572.2
	CH3 HN	(pyrrolidin-3- ylsulfonyl)benzamide	
3734			
3734	N, N CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-	
3735	NH CH <sub>3</sub> HO CH <sub>3</sub>	hydroxypropy1}-3- methyl-5-(4-methyl- 1,2,3-thiadiazol-5- yl)isoxazole-4- carboxamide	
	CH <sub>3</sub> N	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-	
3736	HO NH CH <sub>3</sub>	ethylbenzyl)amino]-2- hydroxypropyl}-5- methyl-2-phenyl-2H- 1,2,3-triazole-4- carboxamide	
	S S N N N CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-	
	HO N	hydroxypropyl}-2-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3-thiazole-4-carboxamide	
3737	CH₃		
	O NH CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-phenylimidazo[1,2-a]pyridine-6-carboxamide	
3738	F—————————————————————————————————————		

3739	F HO HN O CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>5</sup> -(1,3-thiazol-2-yl)pentanediamide	
3740	CH S CH S CH S CH S CH S CH S CH S CH S	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(4-methyl-1,2,3-thiadiazol-5-yl)thio]acetamide	
3741	CH <sub>3</sub> HN OH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-(piperidin-1-ylmethyl)-2-furamide	·
3742	FHO CH <sub>3</sub> NH CH <sub>3</sub> CH <sub>3</sub>	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxamide	

	F HO N CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide	
3743	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-fluoro-4-morpholin-4-	
3744	CH <sub>3</sub> H	ylbenzamide N-{(1S,2R)-1-(3,5-	1 '
	NH S-CH <sub>3</sub>	difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3,5- bis(methylthio)isothi azole-4-carboxamide	
3745	CH₃		,
3746	CH <sub>3</sub> N O NHF F HO NHF CH <sub>3</sub>	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-5-(trifluoromethyl)isoxazole-4-carboxamide	

		37 (/4.5 0=) 4 /0 5	1
	CH³∕	N-{(1S,2R)-1-(3,5-	
	CH <sub>3</sub> CH <sub>3</sub>	difluorobenzyl)-3-  [(3-	
		ethylbenzyl)amino]-2-	
	NH >	hydroxypropyl}-2-	
	√ HN—√ OH	hydroxyplopyl}=2= hydroxy=5=	
	\\\\\\	(propionylamino)benza	
	но У	mide	
:			
3747	F		
	F.	N-{(1S,2R)-1-(3,5-	
	∫ F	difluorobenzyl)-3-	
	OH S	ethylbenzyl)amino]-2-	
	,/	hydroxypropyl}-1-	
	/_NH /	phenyl-1H-pyrrole-2-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	carboxamide	
3748	CH <sub>3</sub>		
	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	,
		difluorobenzyl)-3-	
		[(3-	
	HN—OH F	ethylbenzyl)amino]-2-	
]	=N HN	hydroxypropyl}pyrazin	
		e-2-carboxamide 4- oxide	
	N± %	OVERE	
3749	Ó F		
	₽N,	N-{(1S,2R)-1-(3,5-	
]		difluorobenzyl)-3-	
	CH <sub>3</sub> N	[(3-	,
ļ	, N	ethylbenzyl)amino]-2-	
<u> </u>	O N	hydroxypropyl}-5- methyl-1-pyridin-4-	
	NH /	yl-1H-1,2,3-triazole-	
	FY CH.	4-carboxamide	
	HON		
3750	F		
<u> </u>	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	HN - CIT E	ethylbenzyl)amino]-2-	,
	CH9 OH F	hydroxypropyl}-6-	
	N HN-	methoxypyrazine-2-	
	N±	carboxamide 4-oxide	
3751	oʻ F		,

3752	HO HO NH N-CH <sub>3</sub>	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-phenyl-1H-pyrazole-3-carboxamide	
3732	CH <sub>3</sub> OH NH NH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-hydroxy-3-propylhexanamide	
3753	CH <sub>3</sub>		
	HO Z H H	N-{(1s,2k)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1H-benzimidazole-5-carboxamide	
3754	CH₃ F	N-{(1S,2R)-1-(3,5-	
3755	CH <sub>3</sub> N OH HN OH	difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- hydroxy-4- (propionylamino)benza mide	·

	CI	5-chloro-N-{(1S,2R)-	[
		1-(3,5-	
		difluorobenzyl)-3-	
		[ (3-	
		ethylbenzyl)amino]-2-	
	F 1		
	1 '1 <del> </del>	hydroxypropyl}-1-	
	NH OH	benzofuran-2-	
		carboxamide	
			1
	F NH		
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3756			
3730			
		N-{(1S,2R)-1-(3,5-	
	J 6 J	difluorobenzyl)-3-	
	S H OHH	[(3-	
	I		
	N Y V	ethylbenzyl)amino]-2-	
	) " O • ~ F	hydroxypropyl}-2-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	pyridin-3-yl-1,3-	
		thiazole-4-	
2757	I		
3757	F	carboxamide	
	Ŋ	8-cyano-N-{(1S,2R)-1-	·
	<b>∤</b>	(3,5-difluorobenzyl)-	
		3-[(3-	
	N	1	
!	H	ethylbenzyl)amino]-2-	
]	N.A.F	hydroxypropyl}-4-	
		hydroxyquinoline-3-	
	OH Ö 📐 🤘	carboxamide	
	OH Y	Carboxamide	
	Ì √NH È		
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3758	· [		
		N-1/10 2D) 1 /2 5	
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	N H OH H	[(3-	· ·
		ethylbenzyl)amino]-2-	
1	~ N. \\ ~\		
	l Öla F	hydroxypropyl}-1,6-	
	, YY'	naphthyridine-2-	
		carboxamide	
1			
3759	Í É		
		N-{(1S,2R)-1-(3,5-	
			•
<u> </u>	1 10 0	difluorobenzyl)-3-	
	H OH H	[(3-	
1		ethylbenzyl)amino]-2-	
1		hydroxypropyl}-2,2-	
1		dimethyl-4-	
[		oxochromane-6-	
3760	Ļ	carboxamide	i
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		N (/10 2D) 1 /2 E	
		N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-	
	н онн 🛆	[(3-	
		ethylbenzyl)amino]-2-	•
		hydroxypropyl}-3-	
	N Ö 🌭 F	(morpholin-4-	
		ylmethyl)benzamide	
		yimediyi)benzamide	
3761	i F		
	0′ (	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	H OH H D	[(3-	
	$N \rightarrow N$	ethylbenzyl)amino]-2-	
ļ		hydroxypropyl}-4,7-	
į		dimethoxy-1-	
		benzofuran-5-	
1.50	l Y	carboxamide	
3762	F		
	N CI H OH H	3-chloro-N-{(1S,2R)-	
		1-(3,5-	
		difluorobenzyl)-3-	
	0 VF	[(3-  ethylbenzyl)amino]-2-	i
		hydroxypropyl}-5-	
	Y	phenylisothiazole-4-	
3763	F	carboxamide	
	<del></del>	2-(2,1,3-	
		benzothiadiazol-4-	
		yloxy)-N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	_ لا	3-[(3-	
	HŅ F	ethylbenzyl)amino]-2-	
	HO.	hydroxypropyl}acetami	·
		đe	,
	HŅ F		
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	1 2 N C		
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2764			
3764	<u> </u>	N (/10 2P) 1 /2 5	
	1	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-	
		[(3-	
	CH <sub>3</sub> O F	ethylbenzyl)amino]-2-	
	līŭ I	hydroxypropyl}-2-	
	N V VOH	methoxy-4-	·
		(methylthio)benzamide	
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	ċ <sub>H₃</sub> H		
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3765	CH <sub>3</sub>	·	
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		((4 - 0-) 4 (0 -	
	CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-[(4-	
	HŇ	methyl-1,3-thiazol-2-	
		yl)thio]acetamide	
	S OH		1
	│		
	l s n N		
2766	CH₃ Ţ		
3766	F		
	CH <sub>3</sub> \	N-{(1S,2R)-1-(3,5-	
:		difluorobenzyl)-3-	
		[(3-	
	→ HN— →OH F	ethylbenzyl)amino]-2-	
		hydroxypropyl)-6-	
	CH <sub>3</sub>	methoxy-1-benzofuran-	
		2-carboxamide	
3767	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		,
3,07	CH <sub>3</sub>	5-chloro-N-{(1S,2R)-	,
	0 1	1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	, 'n, Ö	ethylbenzyl)amino]-2-	
	NH HN	hydroxypropyl}-2-	
		morpholin-4-	
		ylbenzamide	
	l c 🙏 ÖH		
-			,
3768			
3700	F F	N-{(1S,2R)-1-(3,5-	
	<b>)</b> ,	difluorobenzy1)-3-	
		[(3-	
	<b>-人</b> -人	ethylbenzyl)amino]-2-	
1	F	hydroxypropyl}-4-	
	HO	methoxy-1H-pyrrole-3-	
1	H NH	carboxamide	
	H NH	Carsonania	
	[		
			,
25.50	<b>L</b>		
3769	CH <sub>3</sub>		
	S	N-{(1S,2R)-1-(3,5-	
1	O CH <sub>3</sub>	difluorobenzyl)-3-	
	]_ N	[(3-	·
1	F	ethylbenzyl)amino]-2-	
	CH <sub>3</sub>	hydroxypropyl}-2-	
	HO HO	methyl-1,3-thiazole-	
3770		4-carboxamide	

N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3-ethylbenzyl) amino] -2-hydroxypropyl) -2-methyl-5-(2-thienyl) -3-furamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3-ethylbenzyl) amino] -2-hydroxypropyl) -4-methoxythiophene -3-carboxamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3-ethylbenzyl) amino] -2-hydroxypropyl) -N-   (3, 5-dimethylpyrazin-2-yl) succinamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3-ethylbenzyl) amino] -2-hydroxypropyl) -N-   (3, 5-dimethylpyrazin-2-yl) succinamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3-ethylbenzyl) amino] -2-hydroxypropyl) -2-   (3, 4-dimethoxyphenyl) thio] acetamide   acetamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio] acetamide   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-((1s, 2r)-1-(3, 5-difluorobenzyl) -3-   (3, 4-dimethoxyphenyl) thio]   N-		<u>,                                     </u>		
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-methyl-5-(2-thienyl)-3-furamide  N-((1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-methoxythiophene-3-carboxamide  N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-N'-(3,5-dimethylpyrazin-2-yl)succinamide  N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-2-[(3,4-dimethoxyphenyl)thio]		H OH H	N-{(1S,2R)-1-(3,5-difluorobenzvl)-3-	
hydroxypropyl)-2- methyl-5-(2-thienyl)- 3-furamide N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-4- methoxythiophene-3- carboxamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-N'- (3,5-dimethylpyrazin- 2-yl)succinamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-2- [(3,4- dimethoxyphenyl)thio]	:	S C F	[(3-	
## Methyl-5-(2-thienyl)- 3-furamide    N-((1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-4-methoxythiophene-3-carboxamide    N-((1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N'-(3,5-dimethylpyrazin-2-yl) succinamide    N-((1s,2R)-1-(3,5-dimethylpyrazin-2-yl) succinamide    N-((1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-2-[(3,4-dimethoxyphenyl) thio]				•
3-furamide N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-methoxythiophene-3-carboxamide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N'-(3,5-dimethylpyrazin-2-yl)succinamide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N'-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[(3,4-dimethoxyphenyl)thio]		· ·		
difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -4- methoxythiophene-3- carboxamide  N-((1s,2R)-1-(3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -N'- (3,5-dimethylpyrazin- 2-yl) succinamide  N-((1s,2R)-1-(3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -2- [(3,4- dimethoxyphenyl) thio]	3771	F	3-furamide	
I (3-ethylbenzyl) amino]-2-hydroxypropyl}-4-methoxythiophene-3-carboxamide				
hydroxypropyl}-4- methoxythiophene-3- carboxamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N'- (3,5-dimethylpyrazin- 2-yl)succinamide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-2- [(3,4- dimethoxyphenyl)thio]				
## The state of th				·
3772    N-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-N'-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1)-3-[(3,4-dimethoxypheny1)thio]	1	HN F		
3772    N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-N'-(3,5-dimethylpyrazin-2-y1)succinamide    N-{(1S,2R)-1-(3,5-dimethylpyrazin-2-y1)succinamide}		1 1 1		
3772    N-{(1S,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-N'-(3,5-dimethylpyrazin-2-y1)succinamide    N-{(1S,2R)-1-(3,5-dimethylpyrazin-2-y1)succinamide}	1			
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-N'-(3,5-dimethylpyrazin-2-y1)succinamide  N-{(1s,2R)-1-(3,5-dimethylpyrazin-2-y1)succinamide}  N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]		O HN F		
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-N'-(3,5-dimethylpyrazin-2-y1)succinamide  N-{(1s,2R)-1-(3,5-dimethylpyrazin-2-y1)succinamide}  N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]				
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N'- (3,5-dimethylpyrazin- 2-yl)succinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- [(3,4- dimethoxyphenyl)thio]	3772	S		
HO HN F ethylbenzyl) amino] -2- hydroxypropyl} -N' - (3,5-dimethylpyrazin- 2-yl) succinamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino] -2- hydroxypropyl} -2- [(3,4- dimethoxyphenyl) thio]				,
hydroxypropyl}-N'- (3,5-dimethylpyrazin- 2-yl) succinamide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- [(3,4- dimethoxyphenyl)thio]			[(3-	,
3773  N-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxyphenyl)thio]		. HN → F		
3773  N-{(1s, 2r)-1-(3, 5-difluorobenzy1)-3-[(3-ethylbenzy1) amino]-2-hydroxypropy1}-2-[(3, 4-dimethoxypheny1) thio]	•	HO		
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]	:	HŅ		
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]		0. O F		
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]		N. VIII		
N-{(1s,2R)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-2-[(3,4-dimethoxypheny1)thio]		J.J.		
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- [(3,4- dimethoxyphenyl)thio]	3773	N \	N-{(15.2R)-1-(3.5-	
ethylbenzyl)amino]-2- hydroxypropyl}-2- [(3,4- dimethoxyphenyl)thio]			difluorobenzyl)-3-	
hydroxypropyl}-2- [(3,4- dimethoxyphenyl)thio]	1			
S [(3,4-dimethoxyphenyl)thio]				
		Ś	[(3,4-	
1 () [10]		NIL.	almethoxyphenyl)thio    acetamide	
OH		1		
NH NH		ŅH		
F \		F F		
3774	3774			

<u></u>			
		N- (1-	
		cyclopropylethyl)-N'-	
		{(1S,2R)-1-(3,5-	
	/	difluorobenzyl)-3-	
	uo HN√ -	[(3-	
	HO, ''' F	ethylbenzyl)amino]-2-	
		hydroxypropyl}-N-	
	HN	phenylsuccinamide	
Į.			
	O TO F		
	\_N		
3775			
	Ę	6-chloro-N-{(1S,2R)-	
ļ	F.F	1-(3,5-	
1		difluorobenzyl)-3-	
	F I I	[(3-	
1	N N	ethylbenzyl)amino]-2-	
1	N OH H CI	hydroxypropyl}-4-	
	H OH CI	(trifluoromethyl)pyri	,
3776		dine-2-carboxamide	3
3770		N-(2-acety1-3-	
	1	thienyl)-N'-{(1S,2R)-	
			•
		1-(3,5-	, 1
		difluorobenzyl)-3-	
	لا	[(3-	
	HŅ	ethylbenzyl)amino]-2-	•
	HO.	hydroxypropyl}succina	
	l I	mide	
	HN N		
	1 7 1		
Į.			·
1	0 0 1		
	F		
	NH		
3777	9_/		1
		N-{(1S,2R)-1-(3,5-	
-	→ → N H OH H →	difluorobenzyl)-3-	(
	F NN NN NN	· ·	
	"   \ \_F	[(3-	
	- Y Y	ethylbenzyl)amino]-2-	
	· · ·	hydroxypropy1}-1-(4-	1
	F	fluorophenyl)-5-	1
		methyl-1H-1,2,4-	
	1	triazole-3-	ł
3778		carboxamide	
	ГО НОНН	$N-\{(1S,2R)-1-(3,5-$	
	1 Setting Nicholand	difluorobenzyl)-3-	
	O H O AF	[(3-	l
	1 Y	ethylbenzyl)amino]-2-	
	Y	hydroxypropyl}-N'-[2-	
	F	fluoro-5-	
		(methylsulfonyl)pheny	1
3779		1] succinamide	
1 4 1 1 3		TIBUCCTHUMITUE	1

		N (/10 2p) 1 /2 5	
	6	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)aminol-2-	
		hydroxypropyl}-4-(4-	
	<u> </u>	methoxyphenyl)thiophe	
		ne-2-carboxamide	
	_S-//		
	NH		
	HO, "\" OH		
	F NH		
Ì			
1 .			
3780			
		N-{(1S,2R)-1-(3,5-	
1	O-S	difluorobenzyl)-3-	
1		[(3-	
		ethylbenzyl)amino]-2-	
	N_0	hydroxypropyl}-4-[5-	
	l ~ <i>I</i>	(methylsulfinyl)-2,3-	
	F	dihydro-1H-indol-1-	
	ONH OH	yl]-4-oxobutanamide	
	ОН		
	F NH	•	
		,	
3781			
	Cl <sub>2</sub> C <sub>2</sub> \ -	2-(acetylamino)-5-	
		chloro-N-{(1S,2R)-1-	
	_ NH	(3,5-difluorobenzyl)-	
	l ₹ \	3-[(3-	
	O'NH OH	ethylbenzyl)amino]-2-	
		hydroxypropyl}thiophe	
	E NIL	ne-3-carboxamide	-
	F NH		
3782			
		N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	l F	ethylbenzyl)amino]-2-	
	HN HN	hydroxypropyl}-2-	
	HO, ""	propyltetrahydro-2H-	
1		pyran-4-carboxamide	•
	HN		
1		•	
3783			
3703	1_/	<u> </u>	

	X	4-chloro-N-{(1S,2R)- 1-(3,5-	
	ا و ا	difluorobenzyl)-3-	
	Ņ H	[(3-	
	CI N F	ethylbenzyl)amino]-2-	
		hydroxypropyl}-7,7- dimethyl-7,8-dihydro-	-
	OH	5H-pyrano[4,3-	
	ZNH F	b]pyridine-2-	
		carboxamide	
3784		0 (0 -1-1 1 ) 27	
		2-(2-chlorophenyl)-N- {(1S,2R)-1-(3,5-	
	CI	difluorobenzyl)-3-	
	l s	[(3-	i
	N ·	ethylbenzyl)amino]-2-	
	l ₹ Ţ	hydroxypropyl}-1,3- thiazole-4-	
	NH OH	carboxamide	
			;
	F NH		
3785	7		
3783	S H OHH	N-{(1S,2R)-1-(3,5-	
1		difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}-2-(3-	
	Ĭ F	methylphenyl)-1,3-	
	·	thiazole-4-	
3786		carboxamide	
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		ethylbenzyl)amino]-2-	•
	HO, HN	hydroxypropyl}-1,2,5-	
1		thiadiazole-3-	
	HN	carboxamide	
	N )		
	S-N O		
	F		
3787	F F	N (/10 0p) 1 /2 F	
	C-Q S H OHH	N-{(1S,2R)-1-(3,5-   difluorobenzyl)-3-	
	N N N N	[(3-	
		ethylbenzyl)amino]-2-	
	\( \forall \)	hydroxypropyl}-2-	
	Ė	(phenoxymethyl)-1,3-	
3788		thiazole-4- carboxamide	
13/00	1	carboxamide	L

	~ ,S¬ н OH н ſ	$N-\{(1S, 2R)-1-(3, 5-$	
	$\rightarrow$ $N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N \rightarrow N $	difluorobenzyl)-3-	
}	" b \ \ \ F	[ (3-	•
	YY'	ethylbenzyl)amino]-2-	
	$\checkmark$	hydroxypropyl}-2-(4-	
Ì	· • • • •	methylphenyl)-1,3-	,
		thiazole-4-	l
200			
3789	·	carboxamide	
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-2-	
	h l l	pyridin-3-ylbenzamide	
	OH	<b>P1224111</b> 4 2 10 4112 11 11 11 11 11 11 11 11 11 11 11 11	
	ĺ √NH É		
,	· · · · ·		
2700	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		
3790		77 ((10 07) 1 (2 5	
		N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	,
	- 11 OH 11	[(3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-4-	
1		methyl-2-phenyl-1,3-	'
	1 Y	oxazole-5-carboxamide	
3791	<u> </u>	•.	
3771		N-{(1s,2R)-1-(3,5-	
	No. of the last of		
	N-N H OH H	difluorobenzyl)-3-	
	I Le V	[(3-	
		ethylbenzyl)amino]-2-	
	1 Y Y	hydroxypropyl}-1-	
1	<b>∀</b> `	ethyl-3-(2-thienyl)-	[
	ļ ģ	1H-pyrazole-5-	
3792		carboxamide	
	F	4-(acetylamino)-N-	
	<b>人</b>	{ (1S, 2R) -1- (3, 5-	
		difluorobenzyl)-3-	
		[(3-	1
	) F	ethylbenzyl)amino]-2-	1
	HN- N N		
	O-N H OHH	hydroxypropyl}-1-	
	1-1-1	methyl-1H-pyrrole-2-	
3793		carboxamide	
	<u> </u>	<del>!</del>	<del></del>

3794	F NH OH NH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2,6-dimethylphenoxy)propanamide	
3795	HZ HZ HZ N-S F	N-{(1s,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-phenyl-1,2,3-thiadiazole-5-carboxamide	: •
3796	S H OH H N F F	N-{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(2,5-dimethyl-1H-pyrrol-1-yl)thiophene-3-carboxamide	
3797	ONH H OH H OH O F	5-(acetylamino)-N- {(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-2- hydroxybenzamide	
3798	F HO CH <sub>3</sub> O CH <sub>3</sub> F O H  O CH <sub>3</sub> F O H	4-(acetylamino)-N- {(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}butanam ide trifluoroacetate	

]	~O O <sub>NS</sub> ,CH₃	N-{(1S,2R)-1-benzy1- 3-[1-ethyl-2-(4-	
	O NHO	methylpentanoyl)hydra	
	N	zino]-2-	
	//,_ NH	hydroxypropyl}-2-	
		[(methylsulfonyl)amin	
1	→ HO →	o]-1,3-oxazole-4- carboxamide	
	HŅŹŅŹCH³	Carbonamiac	
	o 📥		
	CH₃		
	VOI13		
3799	ĊH <sub>3</sub>		
	F I	N-{(1S,2R)-1-(3,5- difluorobenzyl)-3-	519
		[(3-	
		ethylbenzyl)amino]-2-	
	NA COH F	hydroxypropyl}-3-(1-	
	י און די אין ו	methyl-1H-imidazol-2-	
}	CH₃ HN HN	yl)benzamide	
		·	
	CH <sub>3</sub>		
3800			
		N'-[(1S;2R)-3-{[(1R)-	
	H OH H	3-cyclohexyl-1- phenylpropyl]amino}-	
		1-(3,5-	<u> </u>
	_ /=<	difluorobenzyl)-2-	
:		hydroxypropyl]-5-	
	F `F	methyl-N,N- dipropylisophthalamid	
3801	- '	e e	
	CH <sub>3</sub>	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
		difluorobenzyl)-3-	
		[(3- ethylbenzyl)amino]-2-	
İ	NH HN	hydroxypropyl}-N <sup>3</sup> , N <sup>3</sup> -	
	HCI	dipropyl-5-pyridin-3-	
	CH <sub>3</sub> N O OH	ylisophthalamide	
3802	CH <sub>3</sub>	hydrochloride	
3602	F. A.F	N-{(1S,2R)-1-(3,5-	
		difluorobenzy1)-3-	
	он 🖊	[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}-4-	
	NH HN O	fluoro-1-naphthamide	
}	1411114		
	Ĭ. Ž		
3803	CH₃ F	<u>                                     </u>	L

	F	N-cyclohexyl-N'-	1
		$\{(1S, 2R) -1 - (3, 5 -$	1
		difluorobenzyl)-3-	
1		[ (3-	. 1
		ethylbenzyl)amino]-2-	
	T T HHOH H	hydroxypropyl}-N,5-	
	\(\sigma\) \( \)	dimethylisophthalamid	
3804		e	
	ÇH₃	N-{(1S,2R)-1-(3,5-	443.2
1	)	difluorobenzyl)-3-	
		[ (3-	
	( )	ethylbenzyl)amino]-2-	
,		hydroxypropyl}-1-	
	N <sub>2</sub> // <sup>N</sup>	methyl-1H-imidazole-	
	CH <sub>3</sub>	2-carboxamide	
	NH HN	2-Carboxamide	
	o ( )		
	<i>i</i> 7		
	\ OH	·	
	Ϋ́ ν̄́ <sub>F</sub>		:
2005			
3805	F	-1 ((4 5 0 5 ) 4 1 1 7	
		$N^{1}-\{(1S,2R)-1-benzyl-$	·
	H HHOHH	2-hydroxy-3-[(3-	
	N N N N N N N N N N N N N N N N N N N	methoxybenzyl)amino]p	
		ropyl}-N3-	İ
		[oxo(phenyl)methyl]-	i
3806		□-alaninamide	,
	0 04	$N^{1}-\{(1S,2R)-1-benzyl-$	
	Q H <sub>H</sub> QH H ( )	2-hydroxy-3-[(3-	
		methoxybenzyl)amino]p	
1	U	ropyl}-N <sup>2</sup> -	
	1 ~		
		[imino(phenyl)methyl]	]
3807		glycinamide	ļ
	<u> </u>	$N^{1}-\{(1s,2R)-1-(3,5-$	]
	F	difluorobenzyl)-3-	[
		[[(3-	
1		ethylbenzyl)amino]-2-	
	) 0 0 <b>~~</b> F	hydroxypropyl}-N3-(2-	
	し 人 人	propylpentanimidoyl) -	
1	H H OH	D-alaninamide	
		n-araminamine	1
3808			
		6-(4-benzylpiperazin-	
·[	~~N~	1-y1)-N-{(1S,2R)-1-	
		(3,5-difluorobenzyl)-	
	H OH H	2-hydroxy-3-[(3-	
		iodobenzyl)aminolprop	
	0 <b>\_F</b>		
		yl}nicotinamide	
3809	F		
	<u> </u>		·

N-((1s,2R)-1-(3,5-difluorobenzyl)-3- (3-dethylbenzyl) aminol-2-hydroxypropyl)-3- (3-dethylbenzyl) sulfony 1)propanamide   N-((1s,2R)-1-(3,5-difluorobenzyl)-3- (3-dethylbenzyl) minol-2-hydroxypropyl)-5- methyl-7- (trifluoromethyl)pyra zolo(1,5-a)pyrimidine-2- carboxamide   N-((1s,2R)-1-(3,5-difluorobenzyl)-3- (3-dethylbenzyl) minol-2-hydroxypropyl)-N'-(5-phenyl-1,3,4-thiadiazol-2-hydroxypropyl)-N'-(5-phenyl-1,3,4-thiadiazol-2-hydroxypropyl)-3- (3-dethylbenzyl) minol-2-hydroxypropyl)-3- (3-difluorobenzyl)-3- (3-difluoroben				
(3-  ethylbenzyl) amino] -2-  hydroxypropyl) -3-[(3-  methoxyphenyl) sulfony   hydroxypropyl) -3-[(3-  methoxyphenyl) sulfony   hydroxypropyl) -3-[(3-  methoxyphenyl) sulfony   hydroxypropyl) -3-[(3-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-7-  methyl-1,3,4-  methyl-1		F	•	
## OH H    Section   Column		$\rightarrow$	difluorobenzyl)-3-	
## OH H  ##			[(3-	
hydroxypropyl - 3-[(3-methoxyphenyl) sulfony			ethylbenzyl)amino]-2-	
### A Company				
1]propanamide		об нонн 🗸		
N-((1S, 2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-5-methyl-7-(trifluoromethyl) pyra zolo[1,5-z] a]pyrimidine-2-carboxamide		as drawn		
difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) -5- methyl-7- (trifluoromethyl) pyra zolo[1,5- a]pyrimidine-2- carboxamide  N-((1S,2R)-1-(3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl)-N'-(5- phenyl-1,3,4- thiadiazol-2- yl) succinamide  N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1S,2R)-1- (3,5-difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl) succina mide  N-((1S,2R)-1-(3,5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl)-3- (3- ethylbenzyl) amino] -2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- difluorobenzyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl) benzamide	3810			
(3 - ethylbenzyl) amino] -2 - hydroxypropyl) -5 - methyl -7 - (trifluoromethyl) pyra zolo[1,5 - a]pyrimidine -2 - carboxamide				,
## OH H   H	i i	\	difluorobenzyl)-3-	
hydroxypropyl)-5-methyl-7-(trifluoromethyl)pyra zolo(1,5-a)pyrimidine-2-carboxamide   N-(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-N'-(5-phenyl-1,3,4-thiadiazol-2-yl)succinamide   N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N'-(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl} succina mide   N-(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(3-ethylbenzyl) amino]-2-hy		N	[ (3-	
hydroxypropyl}-5- methyl-7- (trifluoromethyl)pyra zolo[1,5- a]pyrimidine-2- carboxamide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl-N'-(5- phenyl-1,3,4- thiadiazol-2- yl)succinamide  N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide		- Дуран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран Суран С	ethylbenzyl)amino]-2-	
methyl-7- (trifluoromethyl)pyra zolo[1,5- a]pyrimidine-2- carboxamide N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N'-(5- phenyl-1,3,4- thiadiazol-2- yl)succinamide N-{5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide			hvdroxvpropv1}-5-	
(trifluoromethyl)pyra zolo[1,5- a]pyrimidine-2- carboxamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl)-N'-(5- phenyl-1,3,4- thiadiazol-2- yl)succinamide  N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1s,2r)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl)succina mide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl)succina mide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide		f `F ``		
Zolo[1,5-a]pyrimidine-2-carboxamide		·		
3811    A   Dyrimidine-2-  carboxamide   N-(1s,2R)-1-(3,5-  difluorobenzyl),73-  (3-  ethylbenzyl)amino]-2-  hydroxypropyl-1,3,4-  thiadiazol-2-  yl) succinamide   N-(5-cyclopropyl-1,3,4-thiadiazol-2-  yl)-N'-(1s,2R)-1-  (3,5-  difluorobenzyl)-3-  (3,5-  difluorobenzyl) amino]-2-  hydroxypropyl) succinamide   N-(1s,2R)-1-(3,5-  difluorobenzyl) amino]-2-  hydroxypropyl) succinamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-  (3-  ethylbenzyl) amino]-2-  hydroxypropyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  dihydro-1H-pyrazol-1-  yl) benzamide   N-(1s,2R)-1-(3,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  difluorobenzyl)-3-(3-  methyl-5-oxo-4,5-  difluorobenzyl)-3-(3-  me				
3811    Carboxamide   N-{(15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl-N'-(5-phenyl-1,3,4-thiadiazol-2-yl) succinamide   N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N'-((15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl) succinamide   N-((15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) benzamide   N-(15,2R)-1-(3,5-dihydro-1H-pyrazol-1-yl) benzamide   N-((15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) benzamide   N-(15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) benzamide   N-(15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(i-intyl) benzamide   N-(15,2R)-1-(3,5-difluorobenzyl)-3-(i(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(i-intyl) benzamide   N-(15,2R)-1-(3,5-difluorobenzyl)-3-(i-intyl) amino]-2-hydroxypropyl)-3-(i-intyl) ami		<u> </u>	= '	
N-{(1s, 2r)-1-(3,5-difluorobenzyl); 3-li(3-ethylbenzyl) amino] -2-hydroxypropyl}-N'-(5-phenyl-1,3,4-thiadiazol-2-yl) succinamide  N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-N'-(1s,2r)-1-(3,5-difluorobenzyl) amino] -2-hydroxypropyl} succinamide  N-(1s,2r)-1-(3,5-difluorobenzyl) amino] -2-hydroxypropyl} succinamide  N-((1s,2r)-1-(3,5-difluorobenzyl) amino] -2-hydroxypropyl} -3-(3-methyl-5-oxo-4,5-dinydro-1H-pyrazol-1-yl) benzamide		r		
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-N'-(5- phenyl-1,3,4- thiadiazol-2- yl)succinamide  N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl)succina mide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide	3811			
(3-ethylbenzyl)amino]-2-hydroxypropyl}-N'-(5-phenyl-1,3,4-thiadiazol-2-yl)succinamide			N-{(1S,2R)-1-(3,5-	
3812    Shape   Hoh Holder   H			difluorobenzyl)-3-	
ethylbenzyl) amino] -2- hydroxypropyl} -N'-(5- phenyl-1, 3, 4- thiadiazol-2- yl) succinamide  N-(5-cyclopropyl- 1, 3, 4-thiadiazol-2- yl)-N'-((1s, 2R)-1- (3, 5-difluorobenzyl) - 3-[(3- ethylbenzyl) amino] -2- hydroxypropyl} succina mide  N-((1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl} succina mide  N-((1s, 2R) -1-(3, 5- difluorobenzyl) -3- [(3- ethylbenzyl) amino] -2- hydroxypropyl} -3-(3- methyl-5-oxo-4, 5- dihydro-1H-pyrazol-1- yl) benzamide		New 20 11 201 11		
hydroxypropyl}-N'-(5- phenyl-1,3,4- thiadiazol-2- yl) succinamide  N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl} succina mide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl) benzamide				
phenyl-1,3,4- thiadiazol-2- yl) succinamide N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-{(1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl} succina mide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl) benzamide		~ sundin		,
## Thiadiazol-2- yl) succinamide    N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl) amino]-2- hydroxypropyl) succina mide    N-((1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl) amino]-2- hydroxypropyl)-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl) benzamide		H 0 <b>\</b> F		,
N-(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,3-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		$\cup$	. — — :	
N-(5-cyclopropyl- 1,3,4-thiadiazol-2- yl)-N'-((1s,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-((1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide	2010	Į.		
1,3,4-thiadiazol-2- yl)-N'-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide	3817	•		,
y1)-N'-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide				
(3,5-difluorobenzyl) - 3-[(3-ethylbenzyl)amino]-2-hydroxypropyl} succina mide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		/	• •	
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succina mide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		\ _		
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}succina mide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide			(3,5-difluorobenzyl)-	
ethylbenzyl)amino]-2- hydroxypropyl}succina mide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide			3-[(3-	
hydroxypropyl}succina mide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		·		
Mide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl)-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	4.	LA HN		
3813  N-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	<b>]</b> .	HU		
3813  N-{(1s,2r)-1-(3,5-difluorobenzy1)-3-[(3-ethylbenzy1)amino]-2-hydroxypropy1}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide	1.	Ι . Γ	made	,
3813  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		HN HN		
3813  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide				
3813  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide				
3813  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		N F		
N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		N. NH , ~~~		٠
N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		l Æs F		
N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		<i>-</i>		
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide	3813	V		
O H OH H ethylbenzyl)amino]-2-hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide				
ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide			difluorobenzyl)-3-	
ethylbenzyl)amino]-2- hydroxypropyl}-3-(3- methyl-5-oxo-4,5- dihydro-1H-pyrazol-1- yl)benzamide			[(3-	
hydroxypropyl}-3-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide		O O H OH H		
methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)benzamide				,
dihydro-1H-pyrazol-1- yl)benzamide		1 \\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \	,	
yl) benzamide		⟩=N Ö <b>V</b> ✓F	: -	1
T I		1/		
3814			AT) penzamide	
	3814	<del> </del>		1

		N-{(1s,2R)-1-(3,5-	
	/	difluorobenzyl)-3-	
}		[(3-	
1		ethylbenzyl)amino]-2-	
	Γ	hydroxypropyl}thieno[	j
	LO HN	2,3-b]quinoline-2-	
	HO, '")	carboxamide	
	Γ	Carboxamice	
<u> </u>	HN		
	$N \sim S$		
2015			
3815	F		
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
	l o	[(3-	
	н онн	ethylbenzyl)amino]-2-	
	H OH H	hydroxypropyl}-1-	
	$N \sim N \sim N$	methyl-5-oxo-2-	
	( ) U \\ \\	phenylprolinamide	
3816	ļ Ļ		
2010	<u> </u>	N (/10 0D) 1 /0 5	
	H OH.	$N-\{(1S,2R)-1-(3,5-$	
	N PH	difluorobenzyl)-3-	
	N O M	[(3-	
1		ethylbenzyl)amino]-2-	
	T > F	hydroxypropyl}-4-	
		methyl-4H,6H-	
1	i <u>+</u>	pyrrolo[1,2-	
	•	a][4,1]benzoxazepine-	
2017			
3817		4-carboxamide	
	<u></u> N	$N-\{(1s,2R)-1-(3,5-$	'
	⟨ .≻w H OHH △	difluorobenzyl)-3-	
	HO N S N N N	[(3-	
ļ	HO N S T	ethylbenzyl)amino]-2-	1
	) YY	hydroxypropyl}-2-[(7-	
	$\vee$	hydroxy-5-	, .
	<u> </u>	methyl[1,2,4]triazolo	
2010		[1,5-a]pyrimidin-2-	
3818		yl)thio]acetamide	
		N-{(1S,2R)-1-(3,5-	
	1	difluorobenzy1)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	•
		hydroxypropyl}-3-oxo-	
		2,3-dihydro-1,2-	
	HŅ	benzisothiazole-6-	
	HO <b>↓</b> J	1	
	Υ	carboxamide 1,1-	
	HN	dioxide	
	ן קון		
	10 4 101		
	I Y F F L	·	
	HN-\$=O F		
3819			
2019	<u> </u>	I	<u> </u>

3820	DH H N F F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}thieno[3,2-c]pyridine-2-carboxamide	·
3821	H OH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carboxamide	
3822	E NH NH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-[oxo(phenoxy)methyl]prolinamide	
3823	H OH H CI O F	6-chloro-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carboxamide	
3824	HO HN-F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-[4-(2,5-dioxopyrrolidin-1-yl)phenoxy]acetamide	

		3	<del></del>
	_	$N^2 - \{(1S, 2R) - 1 - (3, 5 - 1)\}$	
1	Ę	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	·
		hydroxypropyl \ -N\frac{1}{2} -	
	-NH OH ONH	phenylpyrrolidine- 1,2-dicarboxamide	
	NH OH NH	1,2-dicarboxamide	•
3825	/		
		2-(1,3-benzothiazol-	
	н ОН н ┌┐	2-ylmethoxy)-N-	
	$N \sim N \sim N \sim N \sim N \sim N \sim N \sim N \sim N \sim N \sim$	{(1S,2R)-1-(3,5-	
	S O LAF	difluorobenzyl)-3-	
	[ ]	[(3-	
	l Y	ethylbenzyl)amino]-2-	
	<b>├</b>	hydroxypropyl}acetami	
3826		de	<del></del>
		N-{(1S,2R)-1-(3,5-	: 
, .		difluorobenzyl)-3-	
		[(3-	
	H	ethylbenzyl)amino]-2-	
	N. N. A. F	hydroxypropyl}-3-	
		methyl-4-oxo-3,4-	
	O COH	dihydrophthalazine-1-	
	NH F	carboxamide	
			:
3827			
		N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
•	⟨ N¬ H QH H	[(3-	
	N N N	ethylbenzyl)amino]-2-	
	F	hydroxypropyl}indoliz	
		ine-2-carboxamide	
3828	<b> </b>		
	<u> </u>	N-{(1S,2R)-1-(3,5-	
	· О н	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
	Ö	hydroxypropyl}-4-oxo-	
	OH Y	4-phenylbutanamide	
	NH F	_ <del>_</del>	
			]
3829			
3043	L	<u> </u>	<u> </u>

	O-N-O H OH H	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-	
	N N O F	ethylbenzyl)amino]-2- hydroxypropyl}-2-	
	$\sim$	(1,3-dimethyl-2,6-	
	ŧ	dioxo-1,2,3,6- tetrahydro-7H-purin-	
3830		7-yl)acetamide	
3030		N-{(1s,2r)-1-(3,5-	
	Q H	difluorobenzyl)-3-	
	$ HO \longrightarrow N \longrightarrow F $	[(3- ethylbenzyl)amino]-2-	
		hydroxypropy1}-4-(3-	
	NH F	hydroxyphenyl)-4-	
		oxobutanamide	
3831			
3031	I .	N-{(1S,2R)-1-(3,5-	
	О Н	difluorobenzyl)-3-	'
	$N \longrightarrow F$	[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}-4-(3-	
	NH F	methoxyphenyl)-4-	
		oxobutanamide	
3832			
3632	<u> </u>	N-{(1S,2R)-1-(3,5-	
		difluorobenzyl)-3-	
		[(3-	
	H QH H	ethylbenzyl)amino]-2- hydroxypropyl}-3',4'-	
	N N N	dihydro-1'H-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	spiro[1,3-dioxolane-	
	00	2,2'-naphthalene]-8'-	·
		carboxamide	
	į F	·	
3833		N-{(1s,2R)-1-(3,5-	
		difluorobenzyl)-3-	
}		[(3-	,
	h OH H	ethylbenzyl)amino]-2-	
		hydroxypropyl}-3',4'-dihydro-1'H-	
		spiro[1,3-dioxolane-	
		2,2'-naphthalene]-7'-	,
3834	ļ Ė	carboxamide	

2025	S N H O OH F	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -[mercapto(methylthio)methyl]-D-alaninamide	
3835	2 H OH H	N <sup>2</sup> -[(4- chlorophenyl)(oxo)met hyl]-N <sup>1</sup> -{(1S,2R)-1-	
3836	CI H O F	(3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}glycina mide	
	O H N OH F	$N^2-[(4-tert-butylphenyl)(oxo)methyl]-N^1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-$	
3837		hydroxypropyl}glycina mide	:
	HN F	N¹-{(1s,2R)-1-(3,5-difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-N²- [oxo(pyridin-3-y1)methyl]glycinamide	
3838	HN F		

3839	HO HN F	2-{[2-({(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}amino)- 2-oxoethyl]thio)-N- [4-(1,3-oxazol-5- yl)phenyl]acetamide	
2040	HO HN-F	N <sup>2</sup> -[(4- chlorophenyl)(oxo)met hyl]-N <sup>1</sup> -{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-D- alaninamide	
3840	CI H OH H	N <sup>2</sup> -[(3,4-dichlorophenyl)(oxo)methyl]-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}glycinamide	
3842	C H OH H N F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-(5a,9a-dihydrodibenzo[b,d]furan-2-yl)-4-oxobutanamide	. '
3843	HO HN-F HN-NH O F	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -{oxo[4-(trifluoromethyl)phenyl]methyl}glycinamide	

<u></u>			<del></del>
		$N^{1}-\{(1S,2R)-1-(3,5-$	
	E O 11 OH 11 🔨	difluorobenzyl)-3-	l
	F P H OH H []	[(3-	
		= -	·
ĺ	Ĭ <mark>、</mark> 、、∦ 。 、 、 。 。 。	ethylbenzyl)amino]-2-	
	Y F YY	hydroxypropyl}-N2-	
	$\smile$	[(2,6-	
1	<u>L</u> .	difluorophenyl)(oxo)m	
3844	[		
3044		ethyl]glycinamide	
		$N^{1}-\{(1s,2R)-1-(3,5-$	
	о нонн 🔿	difluorobenzyl)-3-	
		[(3-	
	H O V	ethylbenzyl)amino]-2-	
		hydroxypropyl}-N2-	
		[oxo(4-	1
ļ	Ė	methoxyphenyl)methyl]	
2045			
3845		glycinamide	
1		N-{(1S,2R)-1-(3,5-	1
1	$\sim$	difluorobenzyl)-3-	ĺ
	Q N ~	[(3-	
1	T"Y H OH H		
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-4-(2-	
1		oxo-1,3-oxazolidin-3-	
		yl)benzamide	
2046	l Y	yr/benzamrae	
3846	F		
		N-{(1S,2R)-1-(3,5-	
	N	difluorobenzyl)-3-	
		[(3-	'
		1	
	O Conf	ethylbenzyl)amino]-2-	l
		hydroxypropyl}-5-	
	\ \ \ \	(phenylethynyl)nicoti	<u> </u>
3847	ļ Ė	namide	
		N <sup>1</sup> -{(1s,2r)-1-(3,5-	· · · · · · · · · · · · · · · · · · ·
		difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
	1		
Į.	l J	hydroxypropyl}-N3-	
	HO HO F	[oxo(1H-1,2,4-	
		triazol-5-yl)methyl]-	
1		D-alaninamide	'
	HN A	_	1 .
1			İ
1	H HN-		1
	N /		1
	N" >		1
3848	<u>                                    </u>		
1 30 10	14	0 (10 )(//10 00) 1	
		2-{[2-({(1s,2R)-1-	1
		(3,5-difluorobenzyl)-	İ
		3-[(3-	
	HQ HN-	ethylbenzyl)amino]-2-	
·	''` <b>\_</b> ''` F		1
	HN-√ /√	hydroxypropyl amino) -	
	·	2-oxoethyl]thio}-N-	İ
		(pyridin-4-	
	HN(	ylmethyl)acetamide	
3849	N O	1	
	, <del>, , , , , , , , , , , , , , , , , , </del>	•	

		N-{(1S,2R)-1-(3,5-	
	/	difluorobenzyl)-3-	Ì
		ethylbenzyl)amino]-2-	
	( )	hydroxypropyl}-4-	i
		[(methoxymethyl)thio]	ļ
	uo HN√ <sub>E</sub>	benzamide	
	HO, '''' F		
	HN )		
	E		
	s 0 '		l
	0-1		
3850	<i>i</i>		
·		N-{(1s,2R)-1-(3,5-	
	_	difluorobenzy1)-3-	· ]
	$\bigcap_{N} \bigvee_{N$	[(3-	
	) \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	ethylbenzyl)amino]-2-	
	·	hydroxypropyl}-4- (1,5-dimethyl-3-oxo-	
	į Ė	2-phenyl-2,3-dihydro-	
		1H-pyrazol-4-yl)-4-	
3851		oxobutanamide	
3631		4-(4-benzyl-1,4-	
		diazepan-1-yl)-N-	
		{(1s,2R)-1-(3,5-	
	O H OH H	difluorobenzyl)-3-	·
		[(3-	
		ethylbenzyl)amino]-2-	
	Y	hydroxypropyl}-4-	
3852	F	oxobutanamide	
		N-{(1S,2R)-1-(3,5-	
	→ н он н ←	difluorobenzyl)-3-	
		[(3- ethylbenzyl)amino]-2-	
		hydroxypropyl}-2,5-	
		dimethyl-1-(pyridin-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	4-vlmethyl)-1H-	
3853	į Ė	pyrrole-3-carboxamide	
		N-	
	дно н	[(dimethylamino)sulfo	
	I SON NON F	nyl]glycyl-N¹-	
	N O H O L	{(1s,2R)-1-(3,5-	1
		difluorobenzyl)-3-	
	NH F	[(3-	
		ethylbenzyl)amino]-2- hydroxypropyl}glycina	
1		mide	
2054		III. UG	
3854	<u> </u>	<u> </u>	4

N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-4-hydroxycyclohexyl]prolinamide   (2s,3s)-N-((1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide   N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2s,3s)-N-((1s,2r)-1-(3,2r)-1-(3,5-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(3s-dioxopyrrolidin-1-yl)benzamide   (3s-difluorobenzyl)-3-(3s-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)benzamide   (3s-dioxopyrrolidin-1-yl)b
[(3-ethylbenzyl)amino]-2-hydroxypropyl)-4-hydroxycyclohexyl]pro linamide  (2S,3S)-N-((1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
ethylbenzyl)amino]-2- hydroxypropyl}-4- hydroxy-1-[(1R,2R)-2- hydroxycyclohexyl]pro linamide  (2S,3S)-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
hydroxypropyl   -4- hydroxy-1-[(1R, 2R) -2- hydroxycyclohexyl   pro linamide
hydroxypropyl}-4- hydroxy-1-[(1R,2R)-2- hydroxycyclohexyl]pro linamide  (2S,3S)-N-((1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-((1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
hydroxy-1-[(1R,2R)-2-hydroxycyclohexyl]pro linamide   hydroxycyclohexyl]pro linamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-carboxamide   N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,2R)-1-(3,5-difluorobenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,5-difluorobenzyl)-3-(3,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(3,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-dioxopyrrolidin-1-yl)benzamide   (2S,3S)-N-{(1S,2R)-1-(3,5-dioxopyrrolidin-1-
h OH H N OH H N OH hydroxycyclohexyl]pro linamide  (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
3855  OH  (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
3855  OH  (2S,3S)-N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl) amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl) benzamide
(2S,3S)-N-{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide N-{(1S,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
(3,5-difluorobenzyl)- 3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1S,2R)-1-(3,5-difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-methyl-5-oxo-2-pyridin-3-ylpyrrolidine-3-carboxamide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
ethylbenzyl)amino]-2- hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1s,2R)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
hydroxypropyl}-1- methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
methyl-5-oxo-2- pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
pyridin-3- ylpyrrolidine-3- carboxamide  N-{(1s,2r)-1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
ylpyrrolidine-3- carboxamide  N-{(1s,2r)-1-(3,5- difluorobenzy1)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
Garboxamide  N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
N-{(1s, 2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(2,5-dioxopyrrolidin-1-yl)benzamide
difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl)-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
O H OH H ethylbenzyl)amino]-2-hydroxypropyl)-3-(2,5-dioxopyrrolidin-1-yl)benzamide
ethylbenzyl)amino]-2- hydroxypropyl)-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
hydroxypropyl}-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
hydroxypropyl)-3- (2,5-dioxopyrrolidin- 1-yl)benzamide
F (2,5-dioxopyrrolidin- 1-yl)benzamide
1-yl)benzamide
3857
3 Q 5 7
N-(2-cyano-4,5,6,7-
/ tetrahydro-1-
benzothien-3-yl)-N'-
HQ HN- {(1S, 2R) -1-(3,5-
F difluorobenzyl)-3-
HN-\ /=\ [(3-
ethylbenzyl)amino]-2-
mide
3858 N
N-{(1s,2R)-1-(3,5-
difluorobenzyl)-3-
1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
O H OH H ethylbenzyl)amino]-2- hydroxypropyl}-2-
HN Y (2,5-
NH Ö F dioxoimidazolidin-4-
ď [ ] yl)acetamide
3859 F

3860	H OH H N-N O F F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-(5,7-dimethyl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)acetamide	. ,
. 3861	O H H N F F F	N-{(1s,2r)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-1-(2-furylmethyl)-5-oxopyrrolidine-3-carboxamide	
3862	HN OH F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-4-oxo-4-(5-oxo-1,4-diazepan-1-yl)butanamide	
3863	H OH H N H OF F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-5-carboxamide	
3864	O H OH H OH N F F	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2,1,3-benzoxadiazole-5-carboxamide 1-oxide	

		$N-\{(1S, 2R)-1-(3, 5-$	
		difluorobenzyl)-3-	
		[ (3-	
		ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-(2-	
•		pyridin-3-	
. "		ylpiperidin-1-	
3865	F	yl)propanamide	
3003			
		$N-\{(1s,2R)-1-(3,5-$	
	1	difluorobenzyl)-3-	
		[(3-	
		ethylbenzyl)amino]-2-	
	" "		
		hydroxypropyl}-4-oxo-	
	Γ	4-(2-propyl-1H-	
	110 HN - 1	imidazol-1-	'
	HO, '')' F	yl)butanamide	
		y1) bu canalizae	
	/		
	HŅ /		i
	) o F		
	Į.		
	l ✓✓N		, .
			•
3866	N-4		
		$N-\{(1S, 2R)-1-(3, 5-$	
		difluorobenzyl)-3-	
		<del></del>	
		[(3-	
	│ . / H QH H / T	ethylbenzyl)amino]-2-	•
}	NNINI	hydroxypropyl}-4a,9a-	ŀ
4		dihydro-9H-carbazole-	ļ
		9-carboxamide	
		3-carboxamirde	
•			
2067	<u> </u>		
3867	F		<u> </u>
		N-{(1S,2R)-1-(3,5-	
	\_O	difluorobenzyl)-3-	}
	H OH H	[(3-	
	N.N.N.N.N.		
Ì	"	ethylbenzyl)amino]-2-	
		hydroxypropyl}-6-	ĺ
	l LJ	methyl-4-oxo-1-	
1	<b>Y</b>	phenyl-1,4-	
	Į F		,
		dihydropyridazine-3-	l ·
3868		carboxamide	
	0 ^	N'-((1S,2R)-1-(3,5-	
	1	difluorobenzyl)-2-	
	N-√		
		hydroxy-3-{[1-methyl-	1
1	H OH	5-(pyrrolidin-1-	
	N N N NH	ylcarbonyl)-1H-	
i		pyrrol-3-	1
1			1
		yl]amino}propyl)-5-	
1	1	methyl-N,N-	l
1	ļ Ė	dipropylisophthalamid	
1			1
3869	i '	l e · ·	

		N'-((1S,2R)-1-(3,5-	
	$\sim$	difluorobenzyl)-2-	
	O\n\	hydroxy-3-{[2-(2-oxo-	
		2-pyrrolidin-1-	
	HOHHO	ylethoxy)phenyl]amino	
		<pre>}propy1)-5-methy1-</pre>	
		N,N-	
Ì	F→(¯¯)	dipropylisophthalamid	
3870		e	
3870	F F	N'-{(1S,2R)-1-(3,5-	
	Д н онн о П	* * * * * * * * * * * * * * * * * * * *	
	N N N N N N N N N N N N N N N N N N N	difluorobenzyl)-2-	
		hydroxy-3-[(3-{[3-	
1	F-( )	(hydroxymethyl)piperi	
		din-1-	
	<b>'</b>	yl]carbonyl}phenyl)am	
		ino]propyl}-5-methyl-	
1		N, N-	
	•	dipropylisophthalamid	
3871	·	е	
		$N^{1}-\{(1S,2R)-1-(3,5-$	
	о нонн	difluorobenzyl)-3-	•
	N. J. N. J.	[(3-	
	S V N Y V V	ethylbenzyl)amino]-2-	•
	0 \rightarrow F	hydroxypropyl}-N2-[3-	
		(methylthio)-1-	
	ļ ļ	oxopropyl]-N2-	·
3872		pentylglycinamide	
3072	0 11 04 11	N <sup>1</sup> -{(1s,2R)-1-(3,5-	
	O H OH H	difluorobenzyl)-3-	l
	S N Y N Y N Y N Y N Y N Y N Y N Y N Y N	[(3-	
	00 0 0	ethylbenzyl)amino]-2-	
		hydroxypropyl}-N <sup>2</sup> -[3-	1
	ļ		
	•	(methylsulfonyl)-1-	
2072		oxopropyl]-N²-	
3873		pentylglycinamide	ļ
		N-{(1S,2R)-1-benzyl-	
		2-hydroxy-3-[(3-	
	IL J.O. H	methoxybenzyl)amino]p	
	S N	ropyl}-3-	·
1		(phenylsulfonyl)propa	
	O MOH	namide	1
	l L		1
	ŇH		
1			
2074	ų Ψ		
3874		<u> </u>	

3875	O H N HÖH H	N'-{(1S,2R)-1-(3,5-difluorobenzy1)-2-hydroxy-3-[(7-oxabicyclo[2.2.1]hept-2-ylmethyl)amino]propyl}-5-methyl-N,N-dipropylisophthalamide	
3876	H <sub>H</sub> OH H ON I H H ON I H H H OH H H ON I H H H OH H H ON I H H H OH H H OH H H H OH H H H H H H	N'-((1S,2R)-1-(3,5- difluorobenzyl)-2- hydroxy-3-{[(3R)-2- oxo-1-propylazepan-3- yl]amino}propyl)-5- methyl-N,N- dipropylisophthalamid e	
	HHHO H	N'-[(1S,2R)-3-[(1-acetylpiperidin-4-yl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3877	<b>)</b>	,	
3878	N N N N N N N N N N N N N N N N N N N	N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-[2-(dimethylamino)-2-oxoethyl]-N,5-dimethylisophthalamide	
3879	N OH H	N'-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N-[2-(dimethylamino)ethyl]-N-ethyl-5-methylisophthalamide	
3880	N HOH H	N-benzyl-N'-{(1S,2R)- 1-(3,5- difluorobenzyl)-3- [(3- ethylbenzyl)amino]-2- hydroxypropyl}-N,5- dimethylisophthalamid e	

	<del>[</del>	N-{(1S, 2R)-1-(3,5-difluorobenzy1)-3-[(3-	
	OH C	ethylbenzyl)amino]-2-	
		hydroxypropyl}-3-{[2	
	I HOHH	hydroxyethyl)piperidi	
3881	•	n-1-yl]carbonyl}-5- methylbenzamide	
2001		N'-{(1S, 2R)-1-(3,5-	
	F	difluorobenzyl)-3-	
		[(3-	
	N H F	ethylbenzyl)amino]2- hydroxypropyl}-N,5-	
	й бийн й	dimethyl-N-(2-	
2000	<b>'</b>	phenylethyl)isophthal	
3882		amide N'-((1S,2R)-1-(3,5-	
	F	difluorobenzy1)-3-	
		{[3-(3-formyl-2-	
<u>.</u>	O OH F O	furyl)benzyl]amino}-	
	HHOH H	2-hydroxypropyl)-5- methyl-N,N-	,
	, , , , , ,	dipropylisophthalamid	
3883		e	
	F	N'-((1S,2R)-1-(3,5- difluorobenzyl)-3-	
	S <sub>H</sub>	{[3-(5-formyl-2-	
	O OH F S	thienyl)benzyl]amino}	
	H OH H	-2-hydroxypropyl)-5- methyl-N,N-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	dipropylisophthalamid	
3884		е	
		N'-{(1S,2R)-1-(3,5-	,
		difluorobenzyl)-3-	
	F F	ethylbenzyl)amino]-2-	
	I I HOHH ()	hydroxypropyl}-N,5-	
		dimethyl-N-(2- pyridin-2-	
		ylethyl) isophthalamid	
3885		e	
		N'-[(1S,2R)-1-(3,5- difluorobenzyl)-2-	
	1 5 1	hydroxy-3-({[1-	
	HHOH H	(methylsulfonyl)piper	
1 .	N N N N N N N N N N N N N N N N N N N	idin-4-   yl]methyl}amino)propy	
	FY H	1]-5-methyl-N, N-	
		dipropylisophthalamid	
3886	Ė Ė	e	

3887	N H N H N H N H N H N H N H N H N H N H	N¹-{(1S,2R)-1-(3,5-difluorobenzy1)-2-hydroxy-3-[(3-methoxybenzy1)amino]propy1}-N³,N³-diethylpiperidine-1,3-dicarboxamide N¹-{(1S,2R)-1-(3,5-difluorobenzy1)-2-hydroxy-3-[(3-methoxybenzy1)amino]propy1}-N³,N³-dipropylpiperidine-1,3-dicarboxamide	
3889	P S H	N'-((1S,2R)-1-(3,5-difluorobenzy1)-3- {[3-(5-formy1-4-methy1-2-thieny1)benzy1]amino}-2-hydroxypropy1)-5-methy1-N,N-dipropylisophthalamide	
3890	O H. F	N'-((1S,2R)-1-(3,5- difluorobenzy1)-2- hydroxy-3-{[3-(1- phenylviny1)benzy1]am ino}propy1)-5-methy1- N,N- dipropylisophthalamid e	
3891	O O H. F. N H OH H	N'-[(1S,2R)-3-[(3-bicyclo[2.2.1]hept-2-ylbenzyl)amino]-1-(3,5-difluorobenzyl)-2-hydroxypropyl]-5-methyl-N,N-dipropylisophthalamide	
3892	N H H OH H	ethyl 3-[3- ({[(2R,3S)-4-(3,5- difluorophenyl)-3- ({3- [(dipropylamino)carbo nyl]-5- methylbenzoyl}amino)- 2- hydroxybutyl]amino}me thyl)phenyl]propanoat e	

		<del></del>	
		ethyl 4-[3-	
		({[(2R,3S)-4-(3,5-	ì
	<b>^</b> _/ <b>\</b> _/. ¯/	difluorophenyl)-3-	
			1
	- 0 $-$	({3-	
	<b>)</b>	[(dipropylamino)carbo	
	HO. /NH	- · · = ·	
	HO, /-NH	nyl]-5-	
		methylbenzoyl amino) -	
	$H \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow V \rightarrow $	2-	ļ
	HN 1   ]	<del>-</del>	
	П	hydroxybutyl]amino}me	
		thyl)phenyl]butanoate	}
	l l'II d'È		
1	l T		1
			(
1			]
3893			
	<u> </u>	mothyr] (2B) _2 _ [2 _	
ì	1	methyl (2R)-3-[3-	
ļ	Į F	({[(2R,3S)-4-(3,5-	
1		difluorophenyl)-3-({3-	
1		[(dipropylamino)carbon	
	H.I T		
1.		yl]-5-	
	HHOH H	methylbenzoyl}amino)-	
ì	1	2-	
İ	1	_	
İ	]	hydroxybutyl]amino}met	
1		hyl)phenyl]-2-	
2004		methylpropanoate	
3894			
1		ethyl 3'-({[(2R,3S)-4-	
	F	(3,5-difluorophenyl)-	
		3-({3-	Į.
1	Y		
•	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	[(dipropylamino)carbon	
	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	y1]-5-	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	methylbenzoyl}amino)-	
		l '	,
i	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	2-	
		hydroxybutyl]amino}met	1
į	<i>&gt;</i> -√	hyl)biphenyl-2-	
2005	%	1	1
3895		carboxylate	<del> </del>
		2-{1-[2-({(1s,2R)-1-	
	F	(3,5-difluorobenzyl)-	1
1	l Ì	3-[(3-	1 .
ł			1
1		ethylbenzyl)amino]-2-	1
		hydroxypropyl amino) -	1
1		2-	1
	I J HHAHH L		1
`		oxoethyl]cyclopentyl}-	1
3896	] 1	N, N-dipropylacetamide	
<del> </del>	<u> </u>	$N^2$	702
	( )·		1,02
1	CH₃	[(benzyloxy)carbonyl]-	1
1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	
1	I	difluorobenzyl)-3-[(3-	1
ľ	\_\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		1
	NH S O F F	ethylbenzyl)amino]-2-	
İ	0 )	hydroxypropyl}-3-[(1-	1 .
	0=\ F	propylbutyl)sulfonyl]-	
	NH O		1
1	/III-( HN	D, L-alaninamide	1
		trifluoroacetate	1
	F—《》HO	1	
	CH <sub>3</sub>		
3897	\	<u> </u>	
	<del></del>		,

<u> </u>			
3898	CH <sub>3</sub> ONH OSO CH <sub>3</sub>	N <sup>2</sup> - [(benzyloxy)carbonyl]- N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- methylbutyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide	654
3070	ÇH₃	N <sup>2</sup> -	624
	HN HN O O	[(benzyloxy)carbonyl]-N¹-{(1S,2R)-1-(3,5-difluorobenzyl)-3-(cyclopropylamino)-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidetrifluoroacetate	
2000	F F OH		·
3899		N <sup>2</sup> -	638
3900	CH <sub>3</sub> OHN OH F F OH	[(benzyloxy)carbonyl]-N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(cyclopropylmethyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidetrifluoroacetate	
3901	CH <sub>3</sub> OHN OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH F F OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH CH CH CH CH CH CH CH CH CH CH CH CH	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -{[(3S)-tetrahydrofuran-3-yloxy]carbonyl}-3-[(1-propylbutyl)sulfonyl]-L-alaninamidetrifluoroacetate	682

		1	500
		$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	682
		difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	. 1
	OH F A OH	hydroxypropyl}-N2-	ŀ
	}-ÿ-\ HN! /=<	{ [ (3S) -	
	\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \	tetrahydrofuran-3-	
		yloxy]carbonyl}-3-[(1-	Ì
		propylbutyl)sulfonyl]-	
	$\bigvee$	D-alaninamide	
3902		trifluoroacetate	
3902	CH <sub>3</sub> (	N <sup>1</sup> -{(1S, 2R)-1-(3,5-	682
		difluorobenzyl)-3-[(3-	002
	CH <sub>3</sub> HN—	ethylbenzyl)amino]-2-	
	\	hydroxypropyl}-N2-	
	S HN	{[(3s)-	
	S-HN-	tetrahydrofuran-3-	
	) HN b	yloxy]carbonyl}-3-[(1-	•
	CH₃ '" >=0 F	propylbutyl)sulfonyl]-	
		D,L-alaninamide	]
1	**	trifluoroacetate	]
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	) YOH		! . I
3903	, F		
	CH <sub>3</sub> \	$N^{1}-\{(1S,2R)-1-(3,5-$	682
	0.13	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	1
	CH₃	hydroxypropyl}-N2-	
	1 - ( 0 _	{ [ (3R) -	
	O HN-	tetrahydrofuran-3-	
		yloxy]carbonyl}-3-[(1-	
i			1
	) HN O	propylbutyl)sulfonyl]-	
	CH₃ ►O F	D, L-alaninamide	
	_ F	trifluoroacetate	
	\ \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\		
3904	,		
	,CH₃	$N^{1}$ -{ (1S,2R)-1-benzyl-3-	648
	( )—o	[(3-	
		methoxybenzyl)amino]-	
	HN—/	2-hydroxypropyl}-N2-	
1	CH₃ Q →OH	{ [ (3s) -	1
1	S HN S	tetrahydrofuran-3-	ì
	HCI ( )	yloxy]carbonyl}-3-[(1-	
	) HN O	propylbutyl)sulfonyl]-	
,	CH₃O	D, L-alaninamide	
ļ.	9	hydrochloride	
		11, 01 0011101 100	
3905			1

		1 2 2 2 2 2	
		$N^{1}-\{(1S,2R)-1-$	730
	>— HN—	(3,5diflurobenzyl)-3-	
	CH <sub>s</sub> >-OH F .	[ (3-	1
	HN-/ /= F	ethylbenzyl)amino]-2-	,
	OH F-VOH	hydroxypropyl}-N2-	
	NHOS F F	{ [ (3S) -1,1-	
	oʻoʻ \	dioxidotetrahydrothien	
	, ←CH³		
	S=0 chs	-3-yloxy]carbonyl}-3-	
	ő	[(1-	
		propylbutyl)sulfonyl]-	
		D,L-alaninamide	]
3906	· · · · · · · · · · · · · · · · · · ·	trifluoroacetate	
	F	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	698
	l	difluorobenzyl)-3-[(3-	
		ethylbenzyl)amino]-2-	
1	F^\\ 0 \\		l ·
	HO NHCH3 S	hydroxypropyl}-N2-	
	T N T CH3	{ [ (3s) -	
	NH S F OU	tetrahydrothiophen-3-	
	o T P	yloxy]carbonyl}-3-[(1-	
		propylbutyl)sulfonyl]-	•
1	l ÇH₃	D, L-alaninamide	<u> </u>
3907	l l	trifluoroacetate	
3907	CH <sub>3</sub>		COC
ļ	<b>○</b> (	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	696
	F O  F	difluorobenzyl)-3-[(3-	
	O NHCHA F OH	ethylbenzyl)amino]-2-	i
		hydroxypropyl}-N2-	
	)=/	{[tetrahydropyran-4-	
	F HO=  √  √  √  √  √  √  √  √  √  √  √  √  √	yloxy]carbonyl)-3-[(1-	]
	NH CH <sub>3</sub>	propylbutyl)sulfonyl]-	
j		D, L-alaninamide	'
2000	CH <sub>3</sub>	trifluoroacetate	
3908	0.18	The state of the s	EE2
	0 N-S-CH <sub>9</sub>	$N^1 - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	773
	F 0= 0 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	diflourobenzyl)-3-[(3-	
	Q NHCH₃\ F	ethylbenzyl)amino]-2-	· '
<b>1</b>	P OH	hydroxypropyl}-N2-{[1-	
"	f HO={ "	(methylsulfonyl)piperi	
	NH CH <sub>3</sub>	din-4-yloxy]carbonyl}-	,
		3-[(1-	
1	CH₃	propylbutyl)sulfonyl]-	,
	1	D,L-alaninamide	
2000			
3909		trifluoroacetate	
	F	N <sup>2</sup> -{[1-acetylpiperidin-	737
	) o	4-yloxy]carbonyl}-N1-	
	)—сн₃	{ (1S, 2R) -1-(3,5-	
	/N	difluorobenzyl)-3-[(3-	1
1.		ethylbenzyl)amino]-2-	
	CH <sub>3</sub>	hydroxypropyl}-3-[(1-	
	O CH, S.	propylbuty1) sulfony1]-	
	CH <sub>3</sub>		
1	) o=( ( )	D, L-alaninamide	
1	NH >-/	trifluoroacetate	
1	/''\ HN—		1
}	E HO	1	
3910	<u> </u>	1	
	I \_	i .	1

	\ .	$N^{1}-\{(1s,2r)-1-(3,5-$	709
		difluorobenzyl)-3-[(3-	
	CH3 HN-	ethylbenzyl)amino]-2-	
	—	hydroxypropyl}-N2-	
		{[[(3R)-5-	
	) HN "	oxopyrrolidin-3-	
	CĤ₃ ´¨ )=O F	yl]methyl]carbonyl}-3-	
	4	[(1-	, ·
	<b>√</b> F		
		propylbutyl)sulfonyl]-	
	ö F	D, L-alaninamide	ı
3911		trifluoroacetate	
1		$N^{1}-\{ (1S, 2R)-1-benzy1-3-$	668
		[(3-	
	HCI O-	methoxybenzyl)amino]-	
	_ /	2-hydroxypropyl}-N2-	
	O NHCH <sub>3</sub>	[(benzyloxy)carbonyl]-	
	//    //	3-[(1-	
	NH S	propylbutyl)sulfonyl]-	· ·
1	HO-NH -S	D,L-alaninamide	
1		hydrochloride	
1		TIZ OT OCHTOT TOE	
	1911		
3912	CH <sub>3</sub> .		ŀ
	ÇH₃	N <sup>2</sup> -	718
	ا (	[(benzyloxy)carbonyl]-	. = 3
		$N^{1}-((1S,2R)-1-(3,5-$	
		difluorobenzyl)-2-	
	∖ F	hydroxy-3-{[2-(3-	<u> </u>
	CH <sub>8</sub> HN FOH	methoxyphenyl)ethyl]am	
	S HN-		ļ
	S HN F F	ino)propyl)-3-[(1-	
	) HN b	propylbutyl)sulfonyl]-	
	ĆH₃ )≕O F	D,L-alaninamide	,
		trifluoroacetate	
2012	( )		1
3913		rt (/10 2D) 1 /2 F	560
1	A A A A A A A A A A A A A A A A A A A	$N^{1} - \{ (1S, 2R) - 1 - (3, 5 - 1) \}$	562
	CH <sub>3</sub>	difluorobenzyl)-3-[(3-	
	HŅ /// F F	ethylbenzyl)amino]-2-	i
	CH <sub>3</sub> OH	hydroxypropyl}-N2-	
	CH <sub>3</sub> HN O	{ [ (3S) -	1
	1 Y	tetrahydrofuran-3-	Į
	۳٬ <u></u> ۰	yloxy]carbonyl}-D-	
		leucinamide	
3914		trifluoracetate	
	OH OH	$N^{1}$ -{(1S,2R)-1-benzy1-2-	548
	CH <sub>3</sub> N OH	hydroxy-3-[(3-	
	HN - 'HN - ''	methoxybenzyl)amino]pr	
	1	opyl}-N <sup>2</sup> -	
		[(benzyloxy)carbonyl]-	
1	ĊH₃HÑ ✓O	L-leucinamide	·
ľ		hydrochloride	1
3915	1	INVATORNIATIA	1

	0.1	2	660
	CH <sub>30</sub> SFO CH <sub>3</sub> CH <sub>30</sub> SFO CH <sub>3</sub> OH  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>2</sup> - [(benzyloxy)carbonyl]- N <sup>1</sup> -((1S)-1-{(1R)-2- [ethyl(isobutylsulfony 1)amino]-1- hydroxyethyl}-3- methylbutyl)-3-[(1-	662
3916	CH <sub>3</sub> O CH <sub>3</sub> CH <sub>3</sub>	propylbutyl)sulfonyl]- D.L-alaninamide	
· ·		N <sup>2</sup> - [(benzyloxy)carbonyl]- N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-N <sup>5</sup> ,N <sup>5</sup> - dipropyl-L-glutamamide trifluoroacetate	681
3917	F    O		· ·
	S CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>2</sup> - [(benzyloxy)carbony1]- N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzyl)amino]-2- hydroxypropy1)-N <sup>5</sup> ,N <sup>5</sup> - dipropy1-D-glutamamide	681
3918	CH <sub>3</sub>	·	
	HCI HN N N N N N N N N N N N N N N N N N N	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -[(1H-pyrazol-4-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	662
3919	CH <sub>3</sub>		

	HCI CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>2</sup> -[(6-chloropyridin-3-yl)carbonyl]-N <sup>1</sup> - {(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	707
3920		hydrochloride	
		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -[(pyridin-2-yl)carbonyl]-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	673
3921	HCI CH <sub>3</sub> HCI CH <sub>3</sub> NHCH <sub>3</sub> NH S  HO NH CH <sub>3</sub> CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(2-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	686
3923	HCI CH <sub>3</sub> HN OH F  HN OH F  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(3-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	686

3924	HCI ONHCH3	N1-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N2-(4-methylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	686
3924	HCI OH F	N <sup>2</sup> -(3-chlorobenzoyl)- N <sup>1</sup> -{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	706
3925	CH <sub>3</sub> CH <sub>3</sub>		
3926	F——HCi	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(4-methoxybenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	702
3927		N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(4-triflluoromethylbenzoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidehydrochloride	740

<u> </u>	HCI	N <sup>2</sup> -	678
	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	(cyclohexylcarbonyl)- N¹-{(1S,2R)-1-(3,5- difluorobenzyl)-3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	070
3928			
	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>2</sup> (benzoy1)-N <sup>1</sup> - {(1S,2R)-1-(3,5- difluorobenzy1)-3-[(3- ethylbenzy1)amino]-2- hydroxypropy1}-3-[(1- propylbuty1)sulfony1]- D,L-alaninamide	672
3929	F		
	NH CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>1</sup> -{(15,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(phenylacetyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	686
3930	F CH <sub>3</sub> F OH  O NH HN HN  F HO	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(3-phenylpropanoyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamidetrifluoroacetate	700
3931	CHQ	$N^1 - \{ (1S, 2R) - 1 - benzyl - 2 - benzyl$	616
3932	HCI CH <sub>3</sub> HN OH	hydroxy-3-[(3- methoxybenzyl)amino]pr opyl)-N <sup>2</sup> - (cyclopropylacetyl)-3- [(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	010

	`	$N^1 - \{ (1S, 2R) - 1 - benzy1 - 2 - 654 \}$	
		hydroxy-3-[(3-	
	)"\=_/ HN\ F	methoxybenzyl)amino]pr	
	⟨ o	opyl}-N2-	
	CH3 }—III— HN—II /— F 8	[(methylsulfonyl)acety	1
1	HN HN	1]-3-[(1-	1
	oʻ"`>=o`	propylbutyl)sulfonyl]-	ŀ
}	сн <u>\$</u> ∕	D, L-alaninamide	i
3933	Ö	trifluoroacetate	- 1
3933	CHO	$N^{1}$ -{ (1S, 2R) -1-benzyl-2-622	
	Сп		
	CH3	hydroxy-3-[(3-	
	HN—	methoxybenzyl)amino]pr	(
1	1 / - \	opy1}-N <sup>2</sup> -	į
1	HCI O HN HN	[(methylthio)acetyl]-	1
i.		3-[(1-	
:	HN 0	propylbutyl)sulfonyl]-	
ľ	CH₃ )=O S-	D,L-alaninamide	
3934	S	hydrochloride	
	СН	$N^{1}$ -{ (1S, 2R) -1-benzy1-2-634	
		hydroxy-3-[(3-	
	l « »—	methoxybenzyl)amino]pr	. [
1	CH <sub>3</sub> → HN—	opy1}-N <sup>2</sup> -(4-hydroxy-4-	
İ	HCI — OH		
		oxobutanoy1) -3-[(1-	
		propylbutyl)sulfonyl]-	
	CHN 0	D,L-alaninamide	
	)=0 	hydrochloride	
	( он		
3935			
3333	СН	$N^1 - \{ (1S, 2R) - 1 - benzyl - 2 - 647 \}$	
	J	hydroxy-3-[(3-	
		methoxybenzyl)amino]pr	
	CH₃ ₩N—		
	HCI	opy1}-N2-[4-	
	HN	(methylamino) -4-	į
1	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	oxobutanoy1]-3-[(1-	
	CHN O	propylbutyl)sulfonyl]-	
	<b>)</b>	D,L-alaninamide	
	CH <sub>3</sub>	hydrochloride	
	HN—		
3936	%		
	СН	$N^{1}$ -{(1S, 2R)-1-benzy1-2-648	
		hydroxy-3-[(3-	ı
1		methoxybenzyl)amino]pr	
	HCI CH3 Q HN—OH	$ opy1\}-N^2-(4-methoxy-4-$	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	oxobutanoyl)-3-[(1-	1
		propylbutyl)sulfonyl]-	
1	CHN 0	D, L-alaninamide	
	>0	hydrochloride	
	(	myarocurorrae	
	ÇH₃ 〉		
2007	)—ď		
3937	ď		

3938	HCI  CH <sub>3</sub> HN  OH  HN  OH  CH <sub>3</sub> OH  CH <sub>3</sub> OH  OH  CH <sub>3</sub> OH  OH  CH <sub>3</sub> OH  OH  OH  OH  OH  OH  OH  OH  OH  O	N- (methylsulfonyl)glycyl -N¹-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]pr opyl}-3-[(1- propylbutyl)sulfonyl]- D,L-alaninamide hydrochloride	669
3939	HCI OH HN CH3	N <sup>2</sup> -acetyl-N <sup>1</sup> -{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-3-(phenylsulfonyl)-D,L-alaninamidehydrochloride	554
3940	HCI NH HN O	(2S)-2-(4-methoxy-4-oxobutanoyl)amino-N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamidehydrochloride	611
	CH <sub>3</sub>	(2R)-2- {[(benzyloxy)carbonyl]amino}-N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamidehydrochloride	631
3941	HCI		

3942	HCI HO CH <sub>3</sub>	(2R) -2-(3-ethoxy-3-oxopropanoyl) amino-N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl) amino]propyl}-5-oxo-5-piperidin-1-ylpentanamidehydrochloride	611
3943	HCI CH <sub>3</sub> OH HN OH HN OH	N <sup>1</sup> -{(1S,2R)-1-benzyl-3-[(3-methoxybenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(4-methoxy-4-oxobutanoyl)-N <sup>5</sup> ,N <sup>5</sup> -dipropyl-D-glutamamidehydrochloride	627
3944	HCI HCI	(2R)-2-(4-methoxy-4- oxobutanoyl)amino-N- {(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-5-oxo-5- piperidin-1- ylpentanamide hydrochloride	611
3945	HCI HCI	(2R)-2-(5-methoxy-5- oxopentanoyl)amino-N- {(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-5-oxo-5- piperidin-1- ylpentanamide hydrochloride	625
3946	CH <sub>3</sub> HN OH F OH F OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH <sub>3</sub> OH CH CH CH CH CH CH CH CH CH CH CH CH CH	N <sup>2</sup> -[(5-chlorothien-2-yl)sulfonyl]-N <sup>1</sup> - {(1S,2R)-1-(3,5-difluorobenzyl)-3- [(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	748

3947	O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub> O C	N <sup>1</sup> -{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-N <sup>2</sup> -(phenylsulfonyl)-3-[(1-propylbutyl)sulfonyl]-D,L-alaninamide	708
	CH <sub>3</sub> OH OH HN OH	N <sup>2</sup> - [(benzylamino)carbony 1]-N <sup>1</sup> -{(1S,2R)-1- (3,5-difluorobenzyl)- 3-[(3- ethylbenzyl)amino]-2- hydroxypropyl}-3-[(1- propylbutyl)sulfonyl] -D,L-alaninamide	701
3948			
3949	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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3950	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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3951	HCI HO NH CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-2- [(isopentylsulfonyl)m ethyl]succinamide hydrochloride	548
3952	HCI CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> 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3953	HCI  HN  O  NHO  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-2- [(isopentylsulfonyl)m ethyl]-N <sup>4</sup> ,N <sup>4</sup> - dimethylsuccinamide hydrochloride	576
3954	E HO O CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-{[(1-propylbutyl)sulfonyl]methyl}propanamide	693
3955	HCI  HCI  HCI  HCI  HCI  HCI  HCI  HCI	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-3- (ethylsulfonyl)-2- {[(isobutylsulfonyl)a mino]methyl}propanami de hydrochloride	598

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3956	HCI  HO  N  N  N  N  N  N  N  CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-3-(ethylthio)- 2- {[(isobutylsulfonyl)a mino]methyl)propanami de hydrochloride	566
3957	HCI HO CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	ropyl}-2- [(isopentylsulfonyl)a minol-4-	598
3958	HCI CH3 O NH CH3 O NH CH3 O NH	N <sup>1</sup> -{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-N <sup>2</sup> - (isopentylsulfonyl)- L-methioninamide hydrochloride	566
3959	CH <sub>3</sub> CH <sub>3</sub> O O = S = O  HO  HO  CH <sub>3</sub> HCI	S-{3-({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino]-2-[(isopentylsulfonyl)methyl]-3-oxopropyl}ethanethioatehydrochloride	579
3960	HO CH <sub>3</sub> O CH <sub>3</sub> O CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-2-hydroxy-3- [(1- propylbutyl)sulfonyl] propanamide	535

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2061	F HO NH OH	N-{(1S,2R)-1-(3,5-difluorobenzyl)-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-2-hydroxy-4-(phenylsulfonyl)butanamide	561
3961			
	HCI CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-2-hydroxy-4- (isopentylsulfonyl)bu tanamide hydrochloride	521
3962	o_ <sub>CH₃</sub>		
3963	HCI CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-4- (isopentylsulfonyl)- 2-phenoxybutanamide hydrochloride	597
3964	HCI CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-4- (isopentylsulfonyl)- 2-(3- methoxyphenoxy)butana mide hydrochloride	627
3965	HO O F OH S CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub>	3-[1-[({(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}amino]carbonyl]-3-(isopentylsulfonyl)propoxy]benzoic acid trifluoroacetate	641

	ÇH <sub>3</sub>		lees
	0, 1	methyl 3-[1- [({(1S,2R)-1-benzyl-	655
	O CHEH3	2-hydroxy-3-[(3-	
1	ししょ しゅっし	methoxybenzyl)amino]p	
	O NH HN	ropyl amino carbonyl]	
	CH3 \	-3-	
1	ЬOH	(isopentylsulfonyl)pr	
•	HCI	opoxy]benzoate	
3966		hydrochloride	
1		N-{(1S, 2R)-1-benzyl-	527
		2-hydroxy-3-[(3-	
	HO	<pre>methoxybenzyl)amino]p ropyl}-2-hydroxy-4-</pre>	
	H OH	(phenylsulfonyl) butan	
	HCI NH OH	amide hydrochloride	
		•	
	l Y		
3967	O_CH <sub>3</sub>		
1		N-{(1S,2R)-1-benzyl-	495
		2-hydroxy-3-[(3-	
		methoxybenzyl)amino]p	
	HO N S	ropyl}-2-hydroxy-4- (phenylthio)butanamid	
	HCI H OH	e hydrochloride	
	NH O''		
			,
		!	
3968	CH <sub>3</sub>		
		N-{ (1S, 2R) -1-benzyl-	541
		2-hydroxy-3-[(3- methoxybenzyl)amino]p	
	HO S	ropy1}-2-methoxy-4-	
		(phenylsulfonyl) butan	
	HCI NH OCH₃	amide hydrochloride	:
2000			•
3969	CH <sub>3</sub>	N-{(1S,2R)-1-benzyl-	F00
-		2-hydroxy-3-[(3-	509
]		methoxybenzyl)amino]p	
	HO. A.S.	ropyl}-2-methoxy-4-	,
	N N N	(phenylthio)butanamid	
	HCI NH O CH3	e hydrochloride	
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			,
3970	O <sub>_CH3</sub>		
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3971	HCI NH CH <sub>3</sub> CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-4- (phenylsulfonyl)-2- propoxybutanamide hydrochloride	569
39/1	CH <sub>3</sub>		
	HCI NH ON ON ON ON ON ON ON ON ON ON ON ON ON	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-2-(benzyloxy)- 4- (phenylsulfonyl)butan amide hydrochloride	617
3972	CH2		
	HN O O S CH <sub>3</sub>	N-{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-N²- [(benzyloxy)carbonyl] -D,L-methioninamide hydrochloride	566
3974	HO NH NH2 HCI NH NH2  CH3	(2S)-2-amino-N- {(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-5-oxo-5- piperidin-1- ylpentanamide dihydrochloride	497

3975	HCI HCI HCI HCI	(2S)-2-(2-ethoxy-2-oxoethanyl)amino-N- {(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino]propyl}-5-oxo-5-piperidin-1-ylpentanamidedihydrochloride	569
3976	HO NH NH2  HCI HCI OCH3	(2R)-2-amino-N- {(1S,2R)-1-benzyl-2- hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-5-oxo-5- piperidin-1- ylpentanamide dihydrochloride	497
3977	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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3978	CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH <sub>3</sub> CH 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3979	HCI OHO H <sub>2</sub> N HN OH	N <sup>1</sup> -{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-N <sup>2</sup> - [(benzyloxy)carbonyl] -L-aspartamide hydrochloride	549

HCI 3980	CH <sub>3</sub> NH OH CH <sub>3</sub> CH <sub>3</sub>	N <sup>1</sup> -{(1S,2R)-1-benzyl- 2-hydroxy-3-[(3- methoxybenzyl)amino]p ropyl}-N <sup>2</sup> - [(tertbutyloxy)carbon yl]-L-aspartamide hydrochloride	515
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What is claimed is:

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A compound of the formula

or a pharmaceutically acceptable salt thereof wherein where  $R_1$  is:

- (I)  $C_1$ - $C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1$ - $C_3$  alkyl,  $C_3$ - $C_8$  cycloalkyl (optionally substituted with  $C_1$ - $C_3$  alkyl  $C_1$ - $C_3$  alkoxy), -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1$ - $C_3$  alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub>, and -OC=O-NR<sub>1-a</sub>R<sub>1-b</sub>, where R<sub>1-a</sub> and R<sub>1-b</sub> are independently at each occurence-H or  $C_1$ - $C_6$  alkyl,
  - (II)  $-CH_2-S(O)_{0-2}-(C_1-C_6 \text{ alky}^1)$ ,
  - (III)  $-CH_2-CH_2-S(O)_{0-2}-(C_1-C_6 \text{ alkyl})$ ,
- (IV) C<sub>2</sub>-C<sub>6</sub> alkenyl with one or two double bonds,
  15 optionally substituted with one, two or three substituents
  selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N,
  -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub> where R<sub>1-a</sub> and R<sub>1-b</sub> are -H or C<sub>1</sub>-C<sub>6</sub>
  alkyl,
- (V)  $C_2$ - $C_6$  alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1$ - $C_3$  alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub> where R<sub>1-a</sub> and R<sub>1-b</sub> are -H or  $C_1$ - $C_6$  alkyl,
  - $(VI) (CH_2)_{n1} (R_{1-ary1})$  where  $n_1$  is zero or one and where  $R_{1-ary1}$  is phenyl, naphthyl, indanyl, indenyl, dihydronaphthayl, or tetralinyl each of which is optionally substituted with one, two, three, four, or five of the following substituents on the aryl ring:
  - (A)  $C_1$ - $C_6$  alkyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C $\equiv$ N, -CF<sub>3</sub>, and  $C_1$ - $C_3$  alkoxy,

(B)  $C_2-C_6$  alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

- (C)  $C_2-C_6$  optionally substituted with one, two or three substituents selected from the group consisting of -F,  $C_1$ , -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_3$  alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (D) -F, Cl, -Br and -I,
  - (E)  $-C_1-C_6$  haloalkoxy
  - (F)  $-C_1-C_6$  alkoxy
- 10 (G)  $-NR_{N-2}R_{N-3}$ ,
  - (H) -OH,
  - (I) -C≡N,
- (J)  $C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF $_3$ ,  $C_1-C_3$  alkoxy, and -NR $_{1-a}$ R $_{1-b}$ ,
  - (K)  $-CO-(C_1-C_4 \text{ alkyl})$ ,
  - (L)  $-SO_2-NR_{1-a}R_{1-b}$ ,
  - (M) -CO-NR<sub>1-a</sub>R<sub>1-b</sub>,
- 20 (N)  $-SO_2-(C_1-C_4 \text{ alkyl})$ ,
  - $(\text{VII}) \ (\text{CH}_2)_{\text{nl}} (\text{R}_{\text{l-heteroaryl}}) \ \text{where} \ \text{R}_{\text{l-heteroaryl}} \ \text{is selected from}$  the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl,
- phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl,
- naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl,

benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl,

- 5 coumarinyl, isocoumarinyl, chromonyl, chromanonyl, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide,
- 10 pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-
- oxide, indazolyl N-oxide, benzothiazolyl N-oxide,
  benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide,
  thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide,
  benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

where the  $R_{1-heteroaryl}$  group is bonded to  $-(CH_2)_{n1}$  by any ring atom of the parent  $R_{N-heteroaryl}$  group substituted by hydrogen such that the new bond to the  $R_{1-heteroaryl}$  group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, four, or five of:

- (1)  $C_1$ - $C_6$  alkyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH,
  - -SH,  $-NR_{1-a}R_{1-b}$ ,  $-C\equiv N$ ,  $-CF_3$ , and  $C_1-C_3$  alkoxy,
- (2) C<sub>2</sub>-C<sub>6</sub> alkenyl with one or two double bonds, optionally substituted with one, two or three substituents
  30 selected from the group consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (3)  $C_2$ - $C_6$  alkynyl with one or two triple bonds, optionally substituted with one, two or three substituents

selected from the group consisting of -F, -C1, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

- (4) -F, -Cl, -Br and -I,
- (5)  $-C_1-C_6$  haloalkoxy,
- (6)  $-C_1-C_6$  alkoxy
- $(7) -NR_{N-2}R_{N-3}$
- (8) OH,

- (9) -C≡N,
- (10)  $C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - $(11) -CO-(C_1-C_4 \text{ alkyl}),$
  - (12)  $-SO_2-NR_{1-a}R_{1-b}$ ,
- 15 (13)  $-CO-NR_{1-a}R_{1-b}$ ,
  - (14)  $-SO_2-(C_1-C_4 \text{ alkyl})$ , with the proviso that when  $n_1$  is zero  $R_{1-\text{heteroaryl}}$  is not bonded to the carbon chain by nitrogen,
- (VIII) -(CH<sub>2</sub>)<sub>n1</sub>-(R<sub>1-heterocycle</sub>) where n<sub>1</sub> is as defined above and R<sub>1-heterocycle</sub> is selected from the group consisting of morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,
- 25 homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide,
- 30 dithianyl, pyranyl, dihydrofuranyl, pyrrolidinonyl, imidazolidinonyl, imidazolidinondionyl, wherein each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring, and

where the  $R_{1-heterocycle}$  group is bonded by any atom of the parent  $R_{1-heterocycle}$  group substituted by hydrogen such that the new bond to the  $R_{1-heterocycle}$  group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:

- (1)  $C_1-C_6$  alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C $\equiv$ N, -CF<sub>3</sub>, and  $C_1-C_3$  alkoxy,
- 10 (2)  $C_2$ - $C_6$  alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1$ - $C_3$  alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub>,
- (3) C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with one, two or three substituents independently selected from the group 15 consisting of -F, -Cl, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (4) -F, -Cl, -Br and -I,
  - (5)  $C_1-C_6$  alkoxy,
  - (6)  $-C_1-C_6$  haloalkoxy,
- 20 (7)  $-NR_{N-2}R_{N-3}$ ,

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- (8) -OH,
- (9) -C≡N,
- (10)  $C_3$ - $C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH
- $-C \equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,
  - (11)  $-CO-(C_1-C_4 \text{ alkyl})$ ,
  - (12)  $-SO_2-NR_{1-a}R_{1-b}$ ,
  - (13)  $-CO-NR_{1-a}R_{1-b}$ ,
- 30  $(14) -SO_2 (C_1 C_4 \text{ alkyl}),$ 
  - (15) =0, with the proviso that when  $n_1$  is zero  $R_{1-}$  heterocycle is not bonded to the carbon chain by nitrogen; where  $R_2$  is selected from the group consisting of:

(I)-H

(II)  $C_1$ - $C_6$  alkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1$ - $C_3$  alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

- 5 (III)  $-(CH_2)_{0-4}-R_{30}$  where  $R_{30}$  is  $R_{1-aryl}$ ,  $R_{1-heteroaryl}$ , or  $R_{1-heterocycle}$ 
  - (IV)  $C_2$ - $C_6$  alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of
- 10 -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (V)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- 15 (VI)  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

where R3 is selected from the group consisting of:

20 (I)-H,

- (II)  $C_1$ - $C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH,
- -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- 25 (III)  $-(CH_2)_{0-4}-R_{30}$ ,
  - (IV)  $C_2-C_6$  alkenyl,
  - (V)  $C_2-C_6$  alkynyl,
  - (VI)  $-(CH_2)_{0-4}-C_3-C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from
- 30 the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - or  $R_2$  and  $R_3$  are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six,

and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-, -SO<sub>2</sub>-, -NR<sub>N-2</sub>-;  $R_N$  is:

- 5 (I)  $R_{N-1}-X_N-$  where  $X_N$  is selected from the group consisting of:
  - (A) -CO-,
  - (B)  $-SO_2-$ ,
  - (C)  $-(CR'R'')_{1-6}$  wherein
- 10 R' and R" at each occurrence are the same or different and are -H,  $C_1-C_4$  alkyl, phenyl, or pyridyl
  - (D) -CO-(CR'R")\_{1-6}-X\_{N-1} wherein  $X_{N-1}$  is selected from the group consisting of -O-, -S- and -NR'-,
    - (E) a single bond, and
- 15 (F)  $-CO-(CR'R'')_{1-6}$

where  $R_{N-1}$  is selected from the group consisting of:

- (A)  $R_{N-aryl}$  wherein  $R_{N-aryl}$  at each occurrence is independently phenyl; naphthyl; tetralinyl; indanyl; indenyl; dihydronaphthyl; or 6,7,8,9-tetrahydro-5H-
- 20 benzo[a]cycloheptenyl; each of which is optionally substituted
   with 1, 2, or 3 groups that at each occurrence are
   independently:
  - (1)  $C_1\text{--}C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group
- consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1$ - $C_3$  alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>, wherein R<sub>1-a</sub> and R<sub>1-b</sub> at each occurrence are independently H or  $C_1$ - $C_6$  alkyl,
  - (2) OH,
  - (3) -NO<sub>2</sub>,
- 30 (4) -F, -Cl, -Br, -I,
  - (5) -CO<sub>2</sub>H,
  - (6) -C≡N,

 $(7) - (CH_2)_{0-4} - CO - NR_{N-2}R_{N-3} \ \ \text{wherein at each}$  occurence  $R_{N-2}$  and  $R_{N-3}$  are the same or different and are selected from the group consisting of:

(a) -H,

5 (b)  $-C_1-C_8$  alkyl optionally substituted with one substituent selected from the group consisting of:

(i) -OH,

(ii) -NR'R"

(iii) phenyl,

10 (c)  $-C_1-C_8$  alkyl optionally substituted with 1, 2, or 3 groups that are independently -F, -Cl, -Br, or -I,

(d)  $-C_3-C_8$  cycloalkyl,

(e)  $-(C_1-C_2 \text{ alkyl})-(C_3-C_8 \text{ cycloalkyl})$ ,

(f)  $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_3 \text{ alkyl})$ ,

(g)  $-C_2-C_6$  alkenyl,

(h)  $-C_2-C_6$  alkynyl,

(i)  $-C_1-C_6$  alkyl chain with one double bond and one triple bond,

20 (j)  $-R_{1-arv1}$ ,

15

(k) -R<sub>1-heteroaryl</sub>,

(1) -R<sub>1-heterocyle</sub>, or

(m) R<sub>N-2</sub>, R<sub>N-3</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or 25 heteroaryl group, wherein said heterocycloalkyl or heteroaryl group is optionally fused to a benzene, pyridine, or pyrimidine ring, and said groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that at each occurrence are independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -CN, -NO<sub>2</sub>, -NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub> alkyl), N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -OH, -C(O)NH<sub>2</sub>, -C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkyl), C<sub>1</sub>-C<sub>6</sub> alkyl);

$$(8) - (CR'R'')_{0-4}CO-OR'$$

(B)  $-R_{N-heteroaryl}$  where  $R_{N-heteroaryl}$  is selected from the group consisting of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl,

- 5 phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzisothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl,
- naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl,
- benzodioxolyl, triazinyl, henoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl,
- 20 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyridinyl-N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide,
- 25 quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide,
- benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide, imidazopyrazolyl, quinazolinonyl, pyrazopyridyl, benzooxadiazolyl, dihydropyrimidinonyl, and

dihydrobenzfuranonyl, where each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring,

where the  $R_{N-heteroaryl}$  group is bonded by any atom of the parent  $R_{N-heteroaryl}$  group substituted by hydrogen such that the new bond to the  $R_{N-heteroaryl}$  group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted with one, two, three, or four of:

(1) C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one, two or three substituents independently selected from the 10 group consisting of C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

```
(2) -OH,
```

$$(3)$$
 -NO<sub>2</sub>,

15

20

25

(7) 
$$-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$$
,

(8) 
$$-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$$
,

(9) 
$$-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$$
,

(10) 
$$-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$$
,

$$(11) - (CH2)0-4-CO-(C3-C8 cycloalkyl),$$

(12) 
$$-(CH_2)_{0-4}-CO-R_{1-aryl}$$
,

(13) 
$$-(CH_2)_{0-4}-CO-R_{1-heteroaryl}$$
,

$$(14)$$
 -  $(CH2)0-4$ -CO-R<sub>1-heterocycle</sub>,

$$(15) - (CH2)0-4 - CO - RN-4$$

(16) 
$$-(CH_2)_{0-4}-CO_2-R_{N-5}$$

$$(17) - (CH2)0-4 - SO2 - NRN-2RN-3,$$

(18) 
$$-(CH_2)_{0-4}-SO-(aryl C_1-C_8 alkyl)$$
,

$$(19) - (CH2)0-4 - SO2 - (C1 - C12 alkyl),$$

(20) 
$$-(CH_2)_{0-4}-SO_2-(C_3-C_8 \text{ cycloalkyl})$$
,

(21) 
$$-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-O-R_{N-5}$$
,

(22) 
$$-(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-N(R_{N-5})_2$$
,

(23) 
$$-(CH_2)_{0-4}-N-CS-N(R_{N-5})_2$$
,

$$(24) - (CH2)0-4-N(-H or RN-5)-CO-RN-2,$$

```
(25) - (CH<sub>2</sub>)<sub>0-4</sub> - NR<sub>N-2</sub>R<sub>N-3</sub>,
                                  (26) - (CH<sub>2</sub>)<sub>0-4</sub> - R<sub>N-4</sub>,
                                  (27) - (CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),
                                  (28) -(CH_2)_{0-4}-O-P(O)-(OR_{100})_2,
                                  (29) - (CH<sub>2</sub>)<sub>0-4</sub>-O-CO-N(R<sub>N-5</sub>)<sub>2</sub>,
 5
                                  (30) -(CH_2)_{0-4}-O-CS-N(R_{N-5})_2,
                                  (31) -(CH_2)_{0-4}-O-(R_{N-5}),
                                  (32) -(CH_2)_{0-4}-O-(R_{N-5})-COOH,
                                  (33) -(CH_2)_{0-4}-S-(R_{N-5}),
                                  (34) - (CH<sub>2</sub>)<sub>0-4</sub>-O-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally
10
       substituted with one, two, three, four, or five of -F),
                                  (35) C_3-C_8 cycloalkyl,
                                  (36) C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with
       C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C\equivN, -CF<sub>3</sub>, C_1-C_3
       alkoxy, or -NR_{1-a}R_{1-b},
15
                                  (37) C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with
       C_1-C_3 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C\equiv N, -CF_3, C_1-C_3
       alkoxy, or -NR_{1-a}R_{1-b},
                                  (38) -(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}
20
                                  (39) - (CH<sub>2</sub>)<sub>1-4</sub> - C<sub>3</sub> - C<sub>8</sub> cycloalkyl,
                         (C) R_{N-aryl}-W-R_{N-aryl},
                         (D) R<sub>N-aryl</sub>-W-R<sub>N-heteroaryl</sub>,
                         (E) R_{N-aryl}-W-R_{1-heterocycle},
                         (F) R_{N-heteroaryl}-W-R_{N-aryl},
25
                          (G) R<sub>N-heteroary1</sub>-W-R<sub>N-heteroary1</sub>,
                          (H) R<sub>N-heteroaryl</sub>-W-R<sub>1-heterocycle</sub>,
                          (I) R<sub>N-heterocycle</sub>-W-R<sub>N-aryl</sub>,
                          (J) R<sub>N-heterocycle</sub>-W-R<sub>N-heteroaryl</sub>,
                          (K) R<sub>N-heterocycle</sub>-W-R<sub>1-heterocycle</sub>,
30
                                  where W is
                                           (1)
                                                   -(CH_2)_{1-4}-
                                                   -0-,
                                           (2)
                                                   -S(0)_{0-2}-,
                                           (3)
                                           (4) -N(R_{N-5})-,
```

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(5) -CO-; or
```

- (6) a bond;
- (II) -CO-(C<sub>1</sub>-C<sub>10</sub> alkyl) wherein the alkyl is optionally substituted with one two or three substituents independently selected from the group consisting of:
  - (A) -OH,
  - (B)  $-C_1-C_6$  alkoxy,
  - (C)  $-C_1-C_6$  thioalkoxy,
  - (D)  $-CO_2-R_{N-8}$  where  $R_{N-8}$  at each occurrence is
- independently -H,  $C_1$ - $C_6$  alkyl or -phenyl which is optionally substituted with 1 or 2 groups that are independently halogen,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkyl or -C(0)NH<sub>2</sub>,
  - (E)  $-CO-NR_{N-2}R_{N-3}$ ,
  - $(F) -CO-R_{N-4}$
- 15 (G)  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,
  - (H)  $-SO_2-NR_{N-2}R_{N-3}$ ,
  - (I)  $-NH-CO-(C_1-C_6 \text{ alkyl})$ ,
  - (J)  $-NH-CO-O-R_{N-8}$ ,
  - (K)  $-NR_{N-2}R_{N-3}$ ,
- 20 (L)  $-R_{N-4}$ ,
  - (M) -O-CO- $(C_1-C_6 \text{ alkyl})$ ,
  - (N)  $-O-CO-NR_{N-8}R_{N-8}$ ,
  - (0)  $-O-(C_1-C_5 \text{ alkyl})-COOH$ ,
  - (P)  $-O-(C_1-C_6)$  alkyl optionally substituted with one,
- two, or three groups that are independently -F, -CI, -Br, or I),
  - (Q)  $-NH-SO_2-(C_1-C_6 \text{ alkyl})$ ,
  - (R) halogen,
  - (S)  $-N(H \text{ or } R_{N-5}) SO_2 R_{N-2}$ ,
- 30 (T)  $-N(H \text{ or } R_{N-5})-CO-(R_{N-2})$ , and
  - (U)  $-SO_2-R_{N-2}$ ,
  - (V) R<sub>N-aryl</sub>;

(III)  $-CO-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$  wherein each alkyl is unsubstituted or independently substituted with one, two, or three substituents selected from the group consisting of :

- (A) -OH,
- 5 (B)  $-C_1-C_6$  alkoxy,
  - (C)  $-C_1-C_6$  thioalkoxy,
  - (D)  $-CO-O-R_{N-8}$ ,
  - (E)  $-CO-NR_{N-2}R_{N-3}$ ,
  - (F)  $-CO-R_{N-4}$ ,
- 10 (G)  $-SO_2-(C_1-C_8 \text{ alkyl})$ ,
  - (H)  $-SO_2-NR_{N-2}R_{N-3}$ ,
  - (I)  $-NH-CO-(C_1-C_6 \text{ alkyl})$ ,
  - (J)  $-NH-CO-O-R_{N-8}$ ,
  - (K)  $-NR_{N-2}R_{N-3}$ ,
- 15 (L)  $-R_{N-4}$ ,

25

- (M) -O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),
- (N)  $-O-CO-NR_{N-8}R_{N-8}$ ,
- (0)  $-O-(C_1-C_5 \text{ alkyl})-CO_2H$ ,
- (P)  $-O-(C_1-C_6$  alkyl optionally substituted with
- 20 one, two, or three groups that are independently -F, -CI, -Br, or -I),
  - $(Q) \rightarrow NH-SO_2-(C_1-C_6 \text{ alkyl}),$
  - (R) halogen,
  - (S)  $-N(H \text{ or } R_{N-5})-SO_2-R_{N-2}$ ,
  - (T)  $-N(H \text{ or } R_{N-5})-CO-(R_{N-2})$ ,
  - (U)  $-SO_2-R_{N-2}$ , and
  - (V) R<sub>N-aryl</sub>;
  - (IV)  $-CO-(C_1-C_6 \text{ alkyl})-S-(C_1-C_6 \text{ alkyl})$  wherein each alkyl is unsubstituted or substituted with one, two, or three of substituents independently selected from the group consisting of:
    - (A) -OH,
    - (B)  $-C_1-C_6$  alkoxy,
    - (C)  $-C_1-C_6$  thioalkoxy,

```
(D) -CO-O-R_{N-8},
                     (E) -CO-NR_{N-2}R_{N-3},
                     (F) -CO-R<sub>N-4</sub>,
                     (G) -SO_2-(C_1-C_8 \text{ alkyl}),
 5
                     (H) -SO_2-NR_{N-2}R_{N-3},
                     (I) -NH-CO-(C_1-C_6 \text{ alkyl}),
                     (J) -NH-CO-O-R_{N-8},
                     (K) -NR_{N-2}R_{N-3},
                     (L) -R_{N-4},
10
                     (M) -0-CO-(C_1-C_6 \text{ alkyl}),
                     (N) -O-CO-NR_{N-8}R_{N-8},
                     (0) -0-(C_1-C_5 \text{ alkyl})-COOH,
                     (P) -0-(C_1-C_6 alkyl optionally substituted with one,
      two, or three groups that are independently -F, -Cl, -Br, or -
15
      I),
                     (Q) -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl),
                     (R) halogen,
                     (S) -N(H \text{ or } R_{N-5})-SO_2-R_{N-2},
                     (T) -N(H \text{ or } R_{N-5})-CO-(R_{N-2}),
20
                     (U) -SO_2-R_{N-2}, and
                     (V) R<sub>N-aryl</sub>;
              (V) -CO-CH(-(CH_2)_{0-2}-O-R_{N-10})-(CH_2)_{0-2}-(R_{N-aryl} \text{ or } R_{N-heteroaryl})
      wherein
                     R_{N-10} is selected from the group consisting of:
25
                             (1) -H,
                             (2) C_1-C_6 alkyl,
                            (3) C_3-C_8 cycloalkyl,
                             (4) C_2-C_6 alkenyl,
                             (5) C_2-C_6 alkynyl,
30
                             (6) R_{1-aryl},
                             (7) R<sub>N-heteroaryl</sub>,
                             (8) R<sub>N-heterocycle</sub>,
```

(VI)  $-CO-(C_3-C_8$  cycloalkyl) where the cycloalkyl group is optionally substituted with one or two substituents independently selected from the group consisting of:

(A) 
$$-(CH_2)_{0-4}-OH$$
,

5

(B) 
$$-(CH_2)_{0-4}-C_1-C_6$$
 alkoxy,

(C) 
$$-(CH_2)_{0-4}-C_1-C_6$$
 thioalkoxy,

(D) 
$$-(CH_2)_{0-4}-CO-O-R_{N-8}$$
,

(E) 
$$-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$$
,

$$(F) - (CH2)0-4-CO-RN-4,$$

10

(G) 
$$-(CH_2)_{0-4}-SO_2-(C_1-C_8 \text{ alkyl})$$
,

(H) 
$$-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$$
,

(I) 
$$-(CH_2)_{0-4}-NH-CO-(C_1-C_6 \text{ alkyl})$$
,

(J) 
$$-NH-CO-O-R_{N-8}$$
,

(K) 
$$-(CH_2)_{0-4}-NR_{N-2}R_{N-3}$$
,

15

(L) 
$$-(CH_2)_{0-4}-R_{N-4}$$
,

$$(M) -O-CO-(C_1-C_6 \text{ alkyl}),$$

(N) 
$$-O-CO-NR_{N-8}R_{N-8}$$
,

(0) 
$$-0-(C_1-C_6 \text{ alkyl})-CO_2H_1$$

(P) -O-(C1-C6 alkyl optionally substituted with one,

20 two, or three groups that are independently selected from -F, -Cl, -Br, and -I),

$$(Q)$$
 -NH-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl),

- (R) halogen,
- (S)  $-N(H \text{ or } R_{N-5})-SO_2-R_{N-2}$ ,

25 (T) -

(T) 
$$-N(H \text{ or } R_{N-5})-CO-(R_{N-2})$$
,

(U)  $-SO_2-R_{N-2}$ , and

(V) R<sub>N-aryl</sub>;

where Rc is:

(I)  $-C_1-C_{10}$  alkyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH,

-SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, -NR<sub>1-a</sub>R<sub>1-b</sub>, -OC=O NR<sub>1-a</sub>R<sub>1-b</sub>, -S(=O)<sub>0-2</sub> R<sub>1-a</sub>, - NR<sub>1-a</sub>C=O NR<sub>1-a</sub>R<sub>1-b</sub>, -C=O NR<sub>1-a</sub>R<sub>1-b</sub>, and -S(=O)<sub>2</sub> NR<sub>1-a</sub>R<sub>1-b</sub>,

- (II) -(CH<sub>2</sub>)<sub>0-3</sub>-(C<sub>3</sub>-C<sub>8</sub>) cycloalkyl where cycloalkyl can be
  optionally substituted with one, two or three substituents
  independently selected from the group consisting of C<sub>1</sub>-C<sub>3</sub>
  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -Ophenyl, -CO<sub>2</sub>H, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- (III) -(CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-aryl</sub> at each occurrence is

  10 independently phenyl; naphthyl; tetralinyl; indanyl; indenyl;
   dihydronaphthyl; or 6,7,8,9-tetrahydro-5H benzo[a]cycloheptenyl; each of which is optionally substituted
   with 1, 2, or 3 groups that at each occurrence are
   independently:
- 15 (1)  $C_1$ - $C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1$ - $C_3$  alkyl, -F, -Cl, -Br, -I,
  - -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
    - (2) OH,
- 20
- $(3) -NO_2,$
- (4) -F, -Cl, -Br, -I,
- (5)  $-CO_2H$ ,
- (6)  $-C \equiv N$ , and
- (7)  $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3};$
- 25 where  $R_{C-\mathbf{x}}$  and  $R_{C-\mathbf{y}}$  are independently

-H,

 $C_1-C_4$  alkyl optionally substituted with one or two -

C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted with 1, 2, or 3 -

30 F,

OH,

-(CH<sub>2</sub>)<sub>0-4</sub>-C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, and phenyl,

or  $R_{C-x}$  and  $R_{C-y}$  are taken together with the carbon to which they are attached to form a carbocycle of three, four, five, six and seven carbon atoms, optionally where one carbon atom is replaced by a heteroatom selected from the group consisting of -O-, -S-,  $-SO_2-$ ,  $-NR_{N-2}-$  and  $R_{C-aryl}$  is defined as is defined above;

- (IV) -(CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-heteroaryl</sub> where R<sub>C-heteroaryl</sub> at each
  occurrence is independently selected from the group consisting
  of pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl,
  indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl,
  quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl,
  isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl,
  indazolyl, benzoisothiazolyl, benzimidazolyl, benzofuranyl,
  furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl,
  triazolyl, tetrazolyl, oxazolopyridinyl, isothiazolyl,
  naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl,
  isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl,
  isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl,
  isobenzothienyl, benzoxazolyl, pyridopyridinyl,
- benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, henoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl,
- 25 coumarinyl, isocoumarinyl, chromonyl, chromanonyl, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, imidazopyrazolyl, quinazolinonyl,
- 30 pyrazopyridyl, benzooxadiazolyl, dihydropyrimidinonyl, dihydrobenzofuranonyl, pyridinyl-N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-

oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide,

where the  $R_{C-heteroaryl}$  group is bonded by any atom of the parent  $R_{C-heteroaryl}$  group substituted by hydrogen such that the new bond to the  $R_{C-heteroaryl}$  group replaces the hydrogen atom and its bond, where heteroaryl is optionally substituted 1, 2, 3, or 4 groups that are independently:

(1)  $C_1-C_6$  alkyl, optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_3$  alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,

- (2) -OH,
- (3) -NO<sub>2</sub>
- (4) -F, -Cl, -Br, -I,
- (5) -CO-OH,
- 20 (6) -C≡N,

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10

- (7)  $-(CH_2)_{0-4}-CO-NR_{N-2}R_{N-3}$ ,
- (8)  $-(CH_2)_{0-4}-CO-(C_1-C_{12} \text{ alkyl})$ ,
- (9)  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})$ ,
- (10)  $-(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkynyl})$ ,
- 25  $(11)_{3} (CH_{2})_{0-4} CO (C_{3} C_{7} \text{ cycloalkyl}),$ 
  - (12) (CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>1-arvl</sub>,
    - (13)  $-(CH_2)_{0-4}-CO-R_{1-heteroaryl}$ ,
    - (14)  $-(CH_2)_{0-4}-CO-R_{1-heterocycle}$ ,
    - (15)  $-(CH_2)_{0-4}-CO-R_{N-4}$ ,
- 30  $(16) (CH_2)_{0-4} CO O R_{N-5}$ 
  - (17)  $-(CH_2)_{0-4}-SO_2-NR_{N-2}R_{N-3}$ ,
  - (18)  $-(CH_2)_{0-4}-SO-(C_1-C_8 \text{ alkyl})$ ,
  - (19)  $-(CH_2)_{0-4}-SO_{2-}(C_1-C_{12} \text{ alkyl})$ ,
  - (20) (CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl);

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(21) -(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-O-R_{N-5},
                        (22) -(CH_2)_{0-4}-N(H \text{ or } R_{N-5})-CO-N(R_{N-5})_2,
                        (23) -(CH_2)_{0-4}-N-CS-N(R_{N-5})_2,
                        (24) - (CH<sub>2</sub>)<sub>0-4</sub>-N(-H or R<sub>N-5</sub>)-CO-R<sub>N-2</sub>,
 5
                        (25) - (CH<sub>2</sub>)<sub>0-4</sub> - NR<sub>N-2</sub>R<sub>N-3</sub>,
                        (26) - (CH<sub>2</sub>)<sub>0-4</sub>-R<sub>N-4</sub>,
                        (27) - (CH<sub>2</sub>)<sub>0-4</sub>-O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl),
                        (28) - (CH<sub>2</sub>)<sub>0-4</sub>-O-P(O) - (OR<sub>100</sub>)<sub>2</sub>,
                        (29) -(CH_2)_{0-4}-O-CO-N(R_{N-5})_2,
                        (30) - (CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>N-5</sub>)<sub>2</sub>,
10
                        (31) -(CH_2)_{0-4}-O-(R_{N-5}),
                        (32) - (CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>N-5</sub>)-COOH,
                        (33) -(CH_2)_{0-4}-S-(R_{N-5}),
                        (34) - (CH<sub>2</sub>)<sub>0-4</sub>-0-(C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted
15
       with one, two, three, four, or five of -F),
                        (35) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
                        (36) C<sub>2</sub>-C<sub>6</sub> alkenyl optionally substituted with C<sub>1</sub>-C<sub>3</sub>
       alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C\equivN, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, or
       -NR_{1-a}R_{1-b},
                        (37) C<sub>2</sub>-C<sub>6</sub> alkynyl optionally substituted with C<sub>1</sub>-C<sub>3</sub>
20
       alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C\equivN, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, or
       -NR_{1-a}R_{1-b},
                        (38) -(CH_2)_{0-4}-N(-H \text{ or } R_{N-5})-SO_2-R_{N-2}, and
                         (39) -(CH_2)_{1-4}-(C_3-C_8 \text{ cycloalkyl}),
                         (V) -(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-aryl},
25
                         (VI) -(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heteroaryl},
                         (VII) -(CR_{C-x}R_{C-y})_{0-4}-R_{C-heteroaryl}-R_{C-aryl},
                         (VIII) - (CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-heteroaryl</sub>-R<sub>C-heteroaryl</sub>,
                         (IX) -(CR_{C-x}R_{C-y})_{0-4}-R_{C-aryl}-R_{C-heterocycle}, wherein
       R_{C-heterocycle} is selected from the group consisting of
30
       morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide,
        thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl,
       pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl,
        tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl,
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homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide, dithianyl, pyranyl, dihydrofuranyl, pyrrolidinonyl, imidazolidinonyl, imidazolidinondionyl, wherein each of the above is optionally fused to a benzene, pyridine, or pyrimidine ring, and

- where the  $R_{i\text{-heterocycle}}$  group is bonded by any atom of the parent  $R_{i\text{-heterocycle}}$  group substituted by hydrogen such that the new bond to the  $R_{i\text{-heterocycle}}$  group replaces the hydrogen atom and its bond, where heterocycle is optionally substituted with one, two, three or four:
- 15 (1)  $C_1-C_6$  alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -NR<sub>1-a</sub>R<sub>1-b</sub>, -C $\equiv$ N, -CF<sub>3</sub>, and  $C_1-C_3$  alkoxy,
- (2)  $C_2-C_6$  alkenyl optionally substituted with one, two or three substituents selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_3$  alkoxy, -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (3)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
    - (4) -F, -Cl, -Br and -I,
    - (5)  $C_1-C_6$  alkoxy,
    - (6)  $-C_1-C_6$  haloalkoxy,
    - $(7) NR_{N-2}R_{N-3}$
- 30 (8) -OH,

- (9) -C≡N,
- (10)  $C_3$ - $C_7$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of -F, -Cl, -OH, -SH

 $-C \equiv N$ ,  $-CF_3$ ,  $C_1-C_3$  alkoxy, and  $-NR_{1-a}R_{1-b}$ ,

- (11)  $-CO-(C_1-C_4 \text{ alkyl})$ ,
- (12)  $-SO_2-NR_{1-a}R_{1-b}$ ,
- (13)  $-CO-NR_{1-a}R_{1-b}$ ,
- $(14) -SO_2 (C_1 C_4 \text{ alkyl}),$

5

- (15) =0, with the proviso that when  $n_1$  is zero  $R_{1-}$  heterocycle is not bonded to the carbon chain by nitrogen;
  - (X) (CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-heteroaryl</sub>-R<sub>C-heterocycle</sub>,
  - (XI)  $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-aryl}$ ,
- 10 (XII)  $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}-R_{C-heteroaryl}$ ,
  - (XIII) (CR<sub>C-x</sub>R<sub>C-y</sub>)<sub>0-4</sub>-R<sub>C-heterocycle</sub>-R<sub>C-heterocycle</sub>,
  - (XIV)  $-(CR_{C-x}R_{C-y})_{0-4}-R_{C-heterocycle}$ ,
  - (XV)  $-[C(R_{C-1})(R_{C-2})]_{1-3}-CO-N-(R_{C-3})_2$  where  $R_{C-1}$  and  $R_{C-2}$  are the same or different and are selected from the group consisting of:
    - (A) -H.,
  - (B)  $-C_1-C_6$  alkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH,
- 20 -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1</sub>,
  - (C)  $C_2-C_6$  alkenyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_6$  alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- 25 (D)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF $_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl, and -NR $_{1-a}$ R $_{1-b}$ ,
  - (E)  $-(CH_2)_{1-2}-S(O)_{0-2}-(C_1-C_6 \text{ alkyl})$ ,
- 30 (F)  $-(CH_2)_{0-4}-C_3-C_8$  cycloalkyl, optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_6$  alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>
  - (G)  $-(C_1-C_4 \text{ alkyl})-R_{C-aryl}$ ,

- (H)  $-(C_1-C_4 \text{ alkyl})-R_{C-heteroaryl}$ ,
- (I) -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heterocycle</sub>,
- (J) -R<sub>C-heteroaryl</sub>,
- (K) -R<sub>C-heterocycle</sub>,
- 5 (M)  $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C-aryl}$  where  $R_{C-4}$  is -O-, -S-

or

-NR<sub>C-5</sub>- where  $R_{C-5}$  is  $C_1$ - $C_6$  alkyl,

- (N)  $-(CH_2)_{1-4}-R_{C-4}-(CH_2)_{0-4}-R_{C-heteroaryl}$ ,
- (O) -R<sub>C-aryl</sub>,
- 10 and where  $R_{C-3}$  at each occurrence is the same or different and is:
  - (A) -H,
  - (B)  $-C_1-C_6$  alkyl optionally substituted with one, two or three substituents independently selected from the group
- 15 consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -C $\equiv$ 3,  $C_1-C_6$  alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (C)  $C_2$ - $C_6$  alkenyl with one or two double bonds, optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1$ - $C_3$
- 20 alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (D)  $C_2-C_6$  alkynyl optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -
- 25 CF<sub>3</sub>,  $C_1$ - $C_6$  alkoxy, -0-phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (E)  $-(CH_2)_{0-4}-C_3-C_8$  cycloalkyl, optionally substituted with one, two or three substituents independently selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_6$  alkoxy, -O-phenyl, -NR<sub>1-a</sub>R<sub>1-b</sub>,
- $(F) -R_{C-aryl},$ 
  - (G) -R<sub>C-heteroaryl</sub>,
  - (H) -R<sub>C-heterocycle</sub>,
  - (I)  $-(C_1-C_4 \text{ alkyl})-R_{C-aryl}$ ,
  - J)  $(C_1-C_4 \text{ alkyl})-R_{C-\text{heteroaryl}}$ ,

(K) - (C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>C-heterocycle</sub>,

(XVI) -CH(R<sub>C-aryl</sub>)<sub>2</sub>,

(XVII) -CH(R<sub>C-heteroary1</sub>)<sub>2</sub>,

(XVIII) -CH(R<sub>C-aryl</sub>)(R<sub>C-heteroaryl</sub>),

- 5 (XIX) -cyclopentyl, -cyclohexyl, or -cycloheptyl ring fused to R<sub>C-aryl</sub> or R<sub>C-heteroaryl</sub> or R<sub>C-heterocycle</sub>, where one carbon of cyclopentyl, cyclohexyl, or -cycloheptyl is optionally replaced with NH, NR<sub>N-5</sub>, O, S(=0)<sub>0-2</sub>, and where cyclopentyl, cyclohexyl, or -cycloheptyl can be optionally substituted with one or two -10 C<sub>1</sub>-C<sub>3</sub> alkyl, -F, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, =O, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
- (XX)  $C_2-C_{10}$  alkenyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>,  $C_1-C_6$  alkoxy, -O- phenyl, and -NR<sub>1-a</sub>R<sub>1-b</sub>,
  - (XXI)  $C_2-C_{10}$  alkynyl optionally substituted with one, two or three substituents selected from the group consisting of  $C_1-C_3$  alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C $\equiv$ N, -CF $_3$ ,  $C_1-C_6$  alkoxy, -O-phenyl, and -NR $_{1-a}$ R $_{1-b}$ ,
- 20 (XXI)  $-(CH_2)_{0-1}-CHR_{C-6}-(CH_2)_{0-1}-R_{C-aryl}$  where  $R_{C-6}$  is  $-(CH_2)_{0-6}-$ OH,

 $(XXII) - (CH_2)_{0-1} - CHR_{C-6} - (CH_2)_{0-1} - R_{C-heteroaryl},$   $(XXIII) - CH(-R_{C-aryl} \text{ or } R_{C-heteroaryl}) - CO_2(C_1 - C_4 \text{ alkyl}),$   $(XXIV) - CH(-CH_2 - OH) - CH(-OH) - NO_2,$   $(XXV) (C_1 - C_6 \text{ alkyl}) - O - (C_1 - C_6 \text{ alkyl}) - OH,$   $(XXVII) - CH_2 - NH - CH_2 - CH(-O - CH_2 - CH_3)_2,$  (XXVIII) - H,  $(XXIX) - (CH_2)_{0-6} - C(=NR_{1-a})(NR_{1-a}R_{1-b});$ 

R<sub>25</sub> at each occurrence is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkanoyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 groups independently selected from halogen, alkyl, hydroxy, alkoxy, and NH<sub>2</sub>, and -R<sub>26</sub>-R<sub>27</sub>, wherein

 $R_{26}$  is selected from the group consisting of -C(0)-,  $-SO_2-$ ,  $-CO_2-$ , -C(0)NH-, and  $-C(0)N(C_1-C_6$  alkyl)-;

 $R_{27}$  is selected from the group consisting of  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, aryl  $C_1$ - $C_6$  alkyl, heterocycloalkyl, and heteroaryl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halogen, haloalkyl, hydroxyalkyl, -  $C(0)NH_2$ ,  $NH_2$ ,  $NH(C_1$ - $C_6$  alkyl),  $N(C_1$ - $C_6$  alkyl)  $(C_1$ - $C_6$  alkyl), -  $C(0)NH(C_1$ - $C_6$  alkyl), - $C(0)NH(C_1$ - $C_6$  alkyl), - $C(0)NH(C_1$ - $C_6$  alkyl).

## 10 a. A compound of the formula

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Z51

and pharmaceutically acceptable salts thereof wherein m is 0-5;

15 B is aryl or heteroaryl optionally substituted with one or two groups independently selected from  $R_6$ ,  $R'_6$ ,  $R''_6$  and  $R'''_6$ , or

B is cycloalkyl or heterocycloalkyl optionally substituted with one, two, three, four, five, six, seven or eight groups independently selected from R<sub>6a</sub>, R<sub>6b</sub>, R'<sub>6a</sub>, R'<sub>6b</sub>, R''<sub>6a</sub>, R''<sub>6a</sub>, R''<sub>6b</sub>, R'''<sub>6a</sub> and R'''<sub>6b</sub>;

C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>7</sub> alkenyl or C<sub>2</sub>-C<sub>7</sub> alkynyl, each of which is optionally substituted with one, two or three groups selected from -NRR', -SR, -CN, -OCF<sub>3</sub>, -CF<sub>3</sub>, -CONRR', -CO<sub>2</sub>R, -SO<sub>2</sub>NRR', -O-P(=O)(OR)(OR'), -N(R)-C(=O)(R'), -N(R)(SO<sub>2</sub>R'), -SO<sub>2</sub>R, -C(=O)R, -NO<sub>2</sub>,

halogen,  $-(CH_2)_{0-4}$ -aryl, and  $-(CH_2)_{0-4}$ -heteroaryl, or R and R' independently are -H,  $-(C_1-C_{10})$  alkyl,  $-(CH_2)_{0-4}-R_{aryl}$ ,  $-(CH_2)_{0-4}-R_{heteroaryl}$ ,  $-(CH_2)_{0-4}-R_{heteroaryl}$ , or

30  $C_2$ - $C_7$  alkenyl or  $C_2$ - $C_7$  alkynyl, each of which is optionally substituted with one, two or three substituents selected from the group consisting of halogen, -OH,

-SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino, and C<sub>1</sub>-C<sub>6</sub> alkyl, or

- -(CH<sub>2</sub>)<sub>0-4</sub>- C<sub>3</sub>-C<sub>7</sub> cycloalkyl optionally substituted with one, two or three substituents selected from the group consisting of halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, mono- or dialkylamino, and C<sub>1</sub>-C<sub>6</sub> alkyl;
- benzyl where the phenyl ring is optionally substituted with 1-3 groups independently selected from halogen,

  OH, -SH, -C≡N, mono or dialkylamino, C₁-C6 alkoxy, or trifluoromethyl;

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- R<sub>6</sub>, R'<sub>6</sub>, R''<sub>6</sub>, R'''<sub>6</sub>, R<sub>6a</sub>, R<sub>6b</sub>, R'<sub>6a</sub>, R'<sub>6a</sub>, R''<sub>6a</sub>, R''<sub>6a</sub>, R'''<sub>6a</sub> and R'''<sub>6b</sub> independently are -OR, -NO<sub>2</sub>, halogen, -CO<sub>2</sub>R, -C $\equiv$ N, -NRR', -SR, -SO<sub>2</sub>R, -C(=O)R, -OCF<sub>3</sub>, -CF<sub>3</sub>, -CONRR', -SO<sub>2</sub>NRR', -O-P(=O)(OR)(OR'), -N(R)(COR'), -N(R)(SO<sub>2</sub>R'), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-NR<sub>7</sub>R'<sub>7</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(CH<sub>2</sub>)<sub>0-4</sub>-CONRR', -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkenyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>2</sub>-C<sub>12</sub> alkynyl), -(CH<sub>2</sub>)<sub>0-4</sub>-CO-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>aryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heterocyclyl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>aryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R<sub>heterocyclyl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO-(C<sub>1</sub>-C<sub>12</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> Cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-SO<sub>2</sub>-(C<sub>3</sub>-C<sub>7</sub> Cycloalkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-N(H or R<sub>11</sub>)-CO-O-R<sub>11</sub>, -(CH<sub>2</sub>)<sub>0</sub>
- 30  $C_1$ -C<sub>8</sub> alkyl optionally substituted with one, two or three groups independently selected from  $C_1$ -C<sub>6</sub> alkyl, -F, -Cl, -Br, -I, -OR, -NO<sub>2</sub>, -F, -Cl, -Br, -I, -CO<sub>2</sub>R, -C=N, -NRR', -SR, -SO<sub>2</sub>R, -C(=O)R, -OCF<sub>3</sub>, -CF<sub>3</sub>, -CONRR', -SO<sub>2</sub>NRR', -O-P(=O)(OR)(OR'), -N(R)(COR'), -

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N(R)(SO_2R'), -(CH_2)_{0-4}-CO-NR_7R'_7, -(CH_2)_{0-4}-CO-(C_1-C_{12})_{0-4}
                       alkyl), -(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl}), -(CH_2)_{0-4}-CO-(C_2-C_{12} \text{ alkenyl})
                       C_{12} alkynyl), -(CH_2)_{0-4}-CO-(C_3-C_7) cycloalkyl), -(CH_2)_{0-4}
                       _{4}-R<sub>aryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heteroaryl</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>heterocyclyl</sub>, -(CH<sub>2</sub>)<sub>0-</sub>
 5
                       _{4}-CO-R_{aryl}, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-R_{heteroaryl}, -(CH<sub>2</sub>)<sub>0-4</sub>-CO-
                       R_{\text{heterocyclyl}}, -(CH_2)_{0-4}-CO-R_{10}, -(CH_2)_{0-4}-CO-O-R_{11}, -(CH_2)_{0-4}
                       _4-SO_2-NR_7R'_7, -(CH_2)_{0-4}-SO-(C_1-C_8 alkyl), -(CH_2)_{0-4}-SO_2-
                       (C_1-C_{12} \text{ alkyl}), -(CH_2)_{0-4}-SO_2-(C_3-C_7 \text{ cycloalkyl}),
                       -(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-O-R_{11}, -(CH_2)_{0-4}-N(H \text{ or } R_{11})-CO-
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                       N(R_{11})_2, -(CH_2)_{0-4}-N(H \text{ or } R_{11})-CS-N(R_{11})_2, -(CH_2)_{0-4}-N(-H
                       or R_{11})-CO-R_7, -(CH<sub>2</sub>)<sub>0-4</sub>-NR<sub>7</sub>R'<sub>7</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-R<sub>10</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-
                       O-CO-(C_1-C_6 \text{ alkyl}), -(CH_2)_{0-4}-O-P(O)-(O-R_{aryl})_2, -(CH_2)_{0-4}
                       _{4}-O-CO-N(R<sub>11</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-CS-N(R<sub>11</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-O-(R<sub>11</sub>),
                       -(CH_2)_{0-4}-O-(R_{11})-COOH, -(CH_2)_{0-4}-S-(R_{11}), C_3-C_7
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                       cycloalkyl, -(CH_2)_{0-4}-N(-H \text{ or } R_{11})-SO_2-R_7, or -(CH_2)_{0-4}-
                       C<sub>3</sub>-C<sub>7</sub> cycloalkyl, or
                       C_2-C_7 alkenyl or C_2-C_7 alkynyl, each of which is
                               optionally substituted with one, two or three
                               groups independently selected from halogen or -
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                               OH, or
               C<sub>2</sub>-C<sub>7</sub> alkenyl or C<sub>2</sub>-C<sub>7</sub> alkynyl, each of which is optionally
                       substituted with one, two or three groups
                       independently selected from halogen, C1-C3 alkyl,
                       -OH, -SH, -C\equivN, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono-
25
                       or dialkylamino, or
               -(CH_2)_{0-4}-0-(C_1-C_6 \text{ alkyl}), where the alkyl portion is
                       optionally substituted with one, two, three, four, or
                       five of halogen, or
       any two of R_{6a}, R_{6b}, R'_{6a}, R'_{6b}, R''_{6a}, R''_{6b}, R'''_{6a} and R'''_{6b}
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               together are oxo;
       R_7 and R'_7 are the same or different and represent -H, -C<sub>3</sub>-C<sub>7</sub>
               cycloalkyl, -(C_1-C_2 \text{ alkyl})-(C_3-C_7 \text{ cycloalkyl}), -(C_1-C_6)
               alky1)-O-(C_1-C_3 \ alky1), -C_2-C_6 \ alkeny1, -C_2-C_6 \ alkyny1, -C_1-C_1
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C6 alkyl chain with one double bond and one triple bond, or -C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with -OH or -NH<sub>2</sub>; or; -C1-C6 alkyl optionally substituted with one, two or three 5 groups independently selected from halogen; or heterocyclyl optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH- $C_1-C_6$  alky1,  $-SO_2-N(C_1-C_6$  alky1)<sub>2</sub>,  $-SO_2-(C_1-C_4$  alky1), - $CO-NH_2$ ,  $-CO-NH-C_1-C_6$  alkyl, oxo and  $-CO-N(C_1-C_6)$ 10 alkyl)2; or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C1-C3 alkyl, halogen, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or 15 C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or 20 C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three of halogen; aryl or heteroaryl, each of which is optionally substituted with halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> 25  $alkyl, -SO_2-N(C_1-C_6 \ alkyl)_2, -SO_2-(C_1-C_4 \ alkyl), -CO NH_2$ ,  $-CO-NH-C_1-C_6$  alkyl, and  $-CO-N(C_1-C_6$  alkyl)<sub>2</sub>; or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C1-C3 alkyl, halogen, -OH, -SH, -C $\equiv$ N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> 30 alkoxy, amino, and mono- or dialkylamino; or  $C_2-C_6$  alkenyl or  $C_2-C_6$  alkynyl, each of which is optionally substituted with one, two or three groups independently selected from C1-C3 alkyl,

halogen, -OH, -SH, -C $\equiv$ N, -CF $_3$ , C $_1$ -C $_3$  alkoxy, amino, and mono- or dialkylamino; or C $_1$ -C $_6$  alkoxy optionally substituted with one, two or three of halogen;

- 5  $R_{10}$  is heterocyclyl optionally substituted with one, two, three or four groups independently selected from  $C_1$ - $C_6$  alkyl;
  - $R_{11}$  is  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_3-C_7$  cycloalkyl,  $-(CH_2)_{0-2}-R_{aryl}$ , or  $-(CH_2)_{0-2}-R_{heteroaryl}$ ;
- $R_{aryl}$  is aryl optionally substituted with halogen, amino, monoor dialkylamino, -OH, -C $\equiv$ N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alkyl,
  -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, or -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or
  - $C_1-C_6$  alkyl optionally substituted with one, two or three groups independently selected from  $C_1-C_3$  alkyl,
- halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

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- $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl, each of which is optionally substituted with one, two or three groups independently selected from  $C_1$ - $C_3$  alkyl, halogen, OH, -SH, -C $\equiv$ N, -CF $_3$ ,  $C_1$ - $C_3$  alkoxy, amino, and monoor dialkylamino; or
- $C_1$ - $C_6$  alkoxy optionally substituted with one, two or three of halogen;
- R<sub>heteroary1</sub> is heteroary1, each of which is optionally substituted

  25 with halogen, amino, mono- or dialkylamino, -OH, -C≡N, 
  SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH-C<sub>1</sub>-C<sub>6</sub> alky1, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alky1)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>
  C<sub>4</sub> alky1), -CO-NH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alky1, or -CO-N(C<sub>1</sub>-C<sub>6</sub>

  alky1)<sub>2</sub>; or
- C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono- or dialkylamino; or

C<sub>2</sub>-C<sub>6</sub> alkenyl or C<sub>2</sub>-C<sub>6</sub> alkynyl, each of which is optionally
 substituted with one, two or three groups
 independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, halogen, OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino, and mono or dialkylamino; or

C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with one, two or three
 of halogen;

R<sub>heterocyclyl</sub> is heterocyclyl optionally substituted with halogen,
amino, mono- or dialkylamino, -OH, -C≡N, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-NH
C<sub>1</sub>-C<sub>6</sub> alkyl, -SO<sub>2</sub>-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -CONH<sub>2</sub>, -CO-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, =O or -CO-N(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>; or

C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one, two or three
groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl,
halogen, -OH, -SH, -C≡N, -CF<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkoxy, amino,

and mono- or dialkylamino; or

 $C_2$ - $C_6$  alkenyl or  $C_2$ - $C_6$  alkynyl, each of which is optionally substituted with one, two or three groups independently selected from  $C_1$ - $C_3$  alkyl, halogen, - OH, -SH, -C $\equiv$ N, -CF $_3$ ,  $C_1$ - $C_3$  alkoxy, amino, and monoor dialkylamino; or

 $C_1$ - $C_6$  alkoxy optionally substituted with one, two or three of halogen;

 $R_2$  and  $R_3$  are independently hydrogen or  $C_1\text{-}C_6$  alkyl; or  $R_2$  and  $R_3$  taken together with the carbon atom to which they are attached form a 3 or 4-membered ring;  $R_C$  is hydrogen or phenyl optionally substituted with  $C_1\text{-}C_3$ 

3. A compound of the formula

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or a pharmaceutically acceptable salt thereof, wherein

alkyl,  $C_2-C_4$  alkynyl, trifluoromethyl, or  $C_1-C_2$  alkoxy.

R<sub>30</sub> is selected from the group consisting of phenyl, pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl, triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-azafluorenyl, pyridyl, piperidinyl, 5 dihydrocyclopentaquinolinyl, furyl, naphthothienyl, phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxadiaza-cyclopentanaphthalenyl, dihydrobenzodioxepinyl, chromanonyl, chromenonyl, oxazolidinyl, benzophenone, pyrazinyl mono N-oxide, benzofuranyl, pyrazolyl, 10 -isoxazolyl-phenyl, phenyl-triazolyl, benzimidazolyl, indolyl, phenyl-pyrrolyl, chromanyl, isoquinolinyl, thienyl-thienyl, benzothienyl, -phenyl-thiadiazolyl, chromanonyl, quinolinyl, -pyrrolyl-C(0)-phenyl, -phenyl-Ophenyl, -phenyl-oxazolyl, -pyrrolidinonyl-phenyl, -phenyl-15 pyrimidinyl, -phenyl-oxadiazolyl, bicyclo[2.2.1]heptenyl, cyclopentyl, thieno[2,3-b]thiophene, cyclohexyl, -phenylimidazolyl, benzoxazole; dihydro-1H-indolyl; 2,3-dihydrobenzo[b]thiophene 1,1-dioxide; benzo[b]thiophene 1,1dioxide; 2,3-dihydro-benzo[d]isothiazole 1,1-dioxide; -20 phenyl-thiazolyl; -phenyl-pyrazolyl, -phenyl-C(0)piperidyl, -phenyl-C(0)-pyrrolidinyl, -phenyl-isoxazolyl, isoindolyl, purinyl, oxazolyl, thiazolyl, pyridazinonyl, thiazolyl, pyranyl, dihydropyranopyridinyl, diazepanyl, azepanyl, cyclopropyl, dihydronaphthoisoxazolyl, 25. benzoindazolyl, dihydrocyclopentachromenonyl, imidazopyrazolyl, tetrahydrocyclopentachromenonyl, dihydroquinolinonyl, pyridyl N-oxide, isochromanyl, quinazolinonyl, pyrazolopyridinyl, dihydrobenzothiophene dioxide, dihydrofurobenzoisoxazolyl, dihydropyrimidine 30 dionyl, thienopyrazolyl, oxazolyl, tetrahydrocyclopentapyrazolyl, dihydronaphthalenonyl, dihydrobenzofuranonyl, dihydrocyclopentathienyl, tetrahydrocyclopentapyrazolyl, tetrahydropyrazoloazepinyl, indazolyl, tetrahydrocycloheptaisoxazolyl,

tetrahydroindolonyl, pyrrolidinyl, thienopyridinyl, dioxodihydrobenzoisothiazolonyl, triazolopyrimidinyl, thienyl, dihydrothienopyrimidinonyl, benzooxadiazolyl, carbazolyl, chromeno[3,4-d]isoxazolyl, chromanonyl, 5 triazolopyridazinyl, oxazolidinyl, -pyrrolyl-(C1-C6 alkyl)-pyridyl, -pyrrolyl-cyclohexyl, pyrrolidinonyl, dihydropyrazolyl, benzooxadiazolyl mono N-oxide, 1-Hpyridazinonyl, -phenyl-dihydro-1-H-pyrazolidinonyl, phenyl-pyrrolidinyl dione, thienoindolyl, 10 thioxobenzothiazolyl, pyrazolopyridinyl, thiomorpholinyl S-oxide, dihydrofurylbenzisoxazolyl, benzoisothiazolinonyl 1,1-dioxide; tetrahydropyrimidinyl dione, tetrahydrothiopyranylindolyl, benzodioxepinyl, -phenylpyrrazolidinonyl, dihydronaphthyl, tetrahydronaphthyl, 15 isoindolinyl dione, -imidazole-benzyl, -thienedihydrooxazolyl, thienoquinolinyl, -pyrrolidine-phenyl, benzooxazolidinonyl, pyrrolopyridinyl, indanonyl, 1-Himidazo[1,2-b]pyrazolyl, dihydrocyclopenta[b]thienyl, dihydroindazolonyl, tetrahydropyrazoloazepinyl, 20 tetrahydrobenzofuranonyl, thienopyrazolyl, cyclopenta[c]pyrazolyl, tetrahydrocyclopenta[c]pyrazolyl, tetrahydroquinoxalinyl dione, tetrahydroindazolyl, imidazobenzoxazinyl, -phenyl-dihydropyrrolyl dione, -phenyl-O-benzyl, -phenyl-benzyl, 3',4'-dihydro-1'H-25 spiro[[1,3]dioxolane-2,2'-naphthalenyl, wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently selected from the group consisting of

 $C_1-C_{10}$  alkyl optionally substituted with 1 phenyl or 1 CN; OH, hydroxy  $C_1-C_{10}$  alkyl optionally substituted with phenyl or  $(C_1-C_4$  alkyl)phenyl,  $C_1-C_6$  alkoxy optionally substituted with 1 or 2 groups that are independently hydroxy or phenyl; haloalkyl, haloalkoxy,  $(CH_2)_{0-4}$   $C(0)NR_{31}R_{32}$ ,  $-NR_{31}-SO_2-(C_1-C_6$  alkyl) wherein the alkyl

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group is optionally substituted with 1, 2, or 3 groups that are independently halogen or R<sub>33</sub>, -SO<sub>2</sub>-. NH(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with 1 or 2 groups that are independently halogen, OH, alkoxy, or  $R_{33}$ ;  $-(C_1-C_6 \text{ alkyl})-SO_2-(C_1-C_6)$ alkyl) wherein the alkyl group is optionally substituted with 1 or 2 groups that are independently halogen, OH,  $C_1$ - $C_4$  alkoxy, or  $R_{33}$ ; -SO<sub>2</sub>-( $C_1$ - $C_6$  alkyl) wherein the alkyl group is optionally substituted with 1 or 2 groups that are independently OH or C1-C4 alkoxy,  $-SO_2-N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$  wherein each alkyl group is optionally substituted with 1 or 2 groups that are independently halogen, OH or R33;  $-SO_2-NH(C_1-C_6 \text{ alkyl})$ -phenyl wherein the phenyl is optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkoxy or halogen,  $-(C_1-C_6$  alkyl)-O-phenyl,  $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-phenyl,$ triazolidine-3,5-dione, halogen, -NHC(0)NH2, -NHC(O)NH( $C_1$ - $C_6$  alkyl), -NHC(O)N( $C_1$ - $C_6$  alkyl)( $C_1$ - $C_6$ alkyl),  $-N(C_1-C_6 \text{ alkyl})C(O)NH_2$ ,  $-N(C_1-C_6)$  $alkyl)C(0)NH(C_1-C_6 \ alkyl)$ ,  $-N(C_1-C_6 \ alkyl)C(0)N(C_1-C_6$ alkyl)( $C_1-C_6$  alkyl),  $-(C_1-C_6$  alkyl) thienyl,  $-(C_1-C_6)$ alkyl) furanyl,  $-S-(C_1-C_6 \text{ alkyl})$  phenyl,  $-SO_2NR_{31}R_{32}$ , - $C(0)-NR_{31}R_{32}$ ,  $-NR_{31}R_{32}$ , dithiane,  $-NHC(S)NH_2$ ,  $-NHC(S)NH(C_1-C_6 \text{ alkyl})$ ,  $-NHC(S)N(C_1-C_6 \text{ alkyl})$   $(C_1-C_6)$ alkyl), -CO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), tetrahydropyran, phenyl optionally substituted with 1 or 2 groups that are independently F, Cl or Br; pyridine, -C2-C4 alkynylphenyl,  $-0-C_3-C_8$  cycloalkyl,  $-0-(C_1-C_6 \text{ alkyl})-R_{33}$ ; pyrrole optionally substituted with one or two methyl groups; 2,3-dihydro-benzofuran; benzo[1,2,5] oxadiazole,  $-C(0)-(C_1-C_{10} \text{ alkyl})$  wherein the alkyl group is optionally substituted with NH2,  $N(C_1-C_6 \text{ alkyl})$ , or  $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ ; -

C(0)NH-phenyl,  $-C(0)N(C_1-C_6 \text{ alkyl})$ -phenyl, 4,4dimethyl-4,5-dihydro-oxazole, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-Spyridine,  $-(C_1-C_6 \text{ alkyl})-SO_2$ -pyridine,  $-(C_1-C_6)$ thioalkoxy)-pyridine, thiazole optionally substituted 5 with 1 or 2 methyl groups, pyrazole,  $-S-(C_1-C_6 \text{ alkyl})$ wherein the alkyl group is optionally substituted with 1 or 2 groups that are independently CN or OH; indole,  $(C_1-C_6 \text{ thioalkoxy})-(C_1-C_6 \text{ alkyl})$ ,  $C_2-C_8$ alkynyl,  $-(CH_2)_{0-4}-SO_2-(C_1-C_{10} \text{ alkyl})$  wherein the alkyl 10 group is optionally substituted with OH; -NHC(O)NH( $C_3$ - $C_8$  cycloalkyl), -N( $C_1$ - $C_6$  alkyl)C(O)NH( $C_3$ - $C_8$ cycloalkyl),  $-N(C_1-C_6 \text{ alkyl})C(O)N(C_1-C_6 \text{ alkyl})(C_3-C_8)$ cycloalkyl), -NHC(0)N( $C_1$ - $C_6$  alkyl)( $C_3$ - $C_8$  cycloalkyl),  $-(C_1-C_6 \text{ alkoxy})-(C_1-C_6 \text{ thioalkoxy}); -CO_2-(C_1-C_6 \text{ alkyl})$ 15 wherein the alkyl group is optionally substituted with phenyl; -C(0)-furan; and imidazolyl; wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C1-C8 alkyl,  $C_2$ - $C_8$  alkenyl, hydroxy  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$ 20 haloalkyl,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkyl,  $-(CH_2)_{0-4}$ - $SO_2$ - $(C_1$ - $C_6$  alkyl) wherein the alkyl is optionally substituted with 1, 2, 3 or 4 independently selected halogen atoms;  $-(CH_2)_{0-4}-SO_2-imidazolyl$ ,  $-(C_1-C_6 alkyl) C(0)NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-C(0)NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6)$ 25  $alkyl)-C(0)N(C_1-C_6 \ alkyl)(C_1-C_6 \ alkyl), -(C_1-C_6 \ alkyl) NH_2$ ,  $-(C_1-C_6 \text{ alkyl})-NH(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl}) N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl}), -(C_1-C_6 \text{ alkyl})$ phenyl,  $-(C_1-C_6 \text{ alkyl})$ pyridyl, -C(0) furanyl,  $(C_1-C_6 \text{ alkyl})$ tetrahydrofuran, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  $-CO_2-(C_1-C_6 \text{ alkyl})$ ,  $-(C_1-C_6 \text{ alkyl})$ 30 alkyl)-furanyl,  $-(CH_2)_{0-4}-SO_2$ -thienyl, -pyrrolidinylbenzyl,  $-(C_1-C_6 \text{ thioalkoxy})-(C_1-C_6 \text{ alkyl})$ ,  $-C(0)-(C_1-C_6)$  $C_6$  alkyl),  $(C_1-C_6$  alkoxy),  $-(C_2-C_6$  alkenyloxy),  $-(C_1-C_6)$ 

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alkyl)- $CO_2$ -( $C_1$ - $C_6$  alkyl), and -C(0)-piperidinyl optionally substituted with  $C_1$ - $C_6$  alkyl; wherein the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently  $C_1$ - $C_4$  alkyl, hydroxy,  $C_1$ - $C_4$  alkoxy, halogen, or

R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached form a 5, 6, or 7 membered heterocycloalkyl or a 6 membered heteroaryl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(0)NH<sub>2</sub>, -C(0)NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl;

 $R_{33}$  at each occurrence is independently, H,  $NH_2$ ,  $NH(C_1-C_6$  alkyl),  $N(C_1-C_6$  alkyl),  $N(C_1-C_6$  alkyl),  $N(C_1-C_6$  alkyl),  $N(C_1-C_6$  alkyl),  $N(C_1-C_6$  alkyl);

R<sub>35</sub> is phenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -S-phenyl, benzodioxole, thienyl, C<sub>1</sub>-C<sub>6</sub> alkyl, furanyl, imidazolyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl), or (CH<sub>2</sub>)<sub>0-4</sub>CN;

R40 is phenyl, -phenyl-pyridyl, biphenyl, -phenyl-benzothienyl,
-phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, phenyl-isoxazolyl, -C(0)-pyridyl, -(C1-C4 alkyl)-O-C(0)NHphenyl wherein the phenyl is optionally substituted with
1, 2, or 3 halogen atoms; -(C1-C4 alkyl)-O-C(0)N(C1-C6
alkyl)-phenyl, -(C1-C6 alkyl)-phenyl, -(C1-C4 alkyl)-SO2NH2,
-(C1-C4 alkyl)-SO2NH(C1-C6 alkyl), -(C1-C4 alkyl)-SO2N(C1-C6
alkyl)(C1-C6 alkyl), -SO2NH2, -SO2NH(C1-C6 alkyl), -SO2N(C1-C6
alkyl)(C1-C6 alkyl), CN, -(CH2)0-4-(C3-C8 cycloalkyl), (C1-C4 alkyl)-C(0)O-(C1-C4 alkyl), -(C1-C4 alkyl)-R33, C1-C10
alkyl, C2-C8 alkenyl, -(C1-C4 alkyl)-NHC(0)-(C1-C4 alkyl), -

 $(CH_2)_{0-4}-C(O)NH_2$ ,  $-(CH_2)_{0-4}-C(O)NH(C_1-C_6 alkyl)$ ,  $-(CH_2)_{0-4} C(0)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl}), \text{ naphthyl},$ tetrahydronaphthyl, dihydronaphthyl, -(CH<sub>2</sub>)<sub>0-4</sub>-imidazolyl, -(CH<sub>2</sub>)<sub>0-4</sub>-pyrrolidinyl, oxazolidinone 3,4-dihydro-5 benzo[e][1,2]oxathiine 2,2-dioxide, pyrimidinyl, 3,4dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide, pyridyl, or pyrimidyl, alkoxyalkyl, -phenyl-benzothienyl, -phenylcyclohexyl, -phenyl-cyclopentyl, -phenyl-(C1-C6 alkyl)cyclopentyl, -phenyl-(C1-C6 alkyl)-cyclohexyl, -phenyl-10 oxazolyl, furanyl, tetrahydrofuranyl, 7-oxabicyclo[2.2.1]heptyl; -dihydro-1-H-pyrazolidinone-phenyl; -phenyl-bicyclo[2.2.1] heptyl; imidazo[2,1b][1,3]thiazolyl; azepanonyl; piperidinyl,  $-(C_1-C_6 \text{ alkyl})$ piperidinyl; bicyclo[2.2.1] heptyl; chromanonyl,  $-(C_1-C_6)$ 15 alkyl)-morpholinyl; -phenyl-C(0)-piperidinyl; tetrahydrothiazolopyridinyl, -pyrrolo-C(0)-pyrrolidinyl; phenyl-C(0)-phenyl; -phenyl-O-phenyl; -phenyl-O-benzyl; phenyl-tetrahydropyridazinonyl; and -phenyldihydropyridazinonyl; 20 wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen,  $C_1$ - $C_8$  alkyl optionally substituted with 1 or two groups that are independently CN or OH; C1-C6 alkoxy, halo  $(C_1-C_8 \text{ alkyl})$ , halo  $(C_1-C_4 \text{ alkoxy})$ , -0-25  $(C_1-C_4 \text{ alkyl})$ -phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, CN, -CHO,  $C_1$ - $C_4$ thioalkoxy,  $-NHSO_2-(C_1-C_6 \text{ alkyl})$ ,  $-N(C_1-C_4 \text{ alkyl})SO_2 (C_1-C_4 \text{ alkyl})$  wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH; -SO<sub>2</sub>R<sub>33</sub>; 30  $R_{33}$ ;  $C_2$ - $C_8$  alkynyl;  $C_2$ - $C_8$  alkenyl; thioalkoxyalkyl; - $SO_2-(C_1-C_{10} \text{ alkyl}); -NR_{31}R_{32}; -C(O)-NR_{31}R_{32}; -OC(O)R_{33};$  $C_1-C_8$  alkanoyl; and  $-(C_1-C_6$  alkyl) $-C(0)-(C_1-C_6$  alkoxy),  $-C(0)-(C_1-C_6 \text{ alkoxy}); -O-(C_1-C_6 \text{ alkyl})-C(0)NR_{31}R_{32}; CO_2-(C_1-C_6 \text{ alkyl});$ 

R<sub>41a</sub> and R<sub>41</sub> are independently H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy, C<sub>1</sub>-C<sub>4</sub> thioalkoxy C<sub>1</sub>-C<sub>6</sub> alkyl; or -C<sub>1</sub>-C<sub>6</sub> alkyl-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl;

5 R<sub>40</sub>, R<sub>41</sub>, and the atom to which they are attached form a C<sub>3</sub>-C<sub>8</sub> cycloalkyl ring which is optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, -CO<sub>2</sub>NH<sub>2</sub>, -CO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), or -CO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); a thiazolyl ring which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl; isoxazolyl ring which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkyl; phenyl which is optionally substituted with 1, 2, or 3 groups that are independently halogen or C<sub>1</sub>-C<sub>6</sub> alkyl; pyrrolidinyl-benzyl; piperidinyl optionally substituted with 1 or 2 groups that are independently -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl) or -C(0)-(C<sub>1</sub>-C<sub>6</sub> alkyl);

and

- $R_{42}$  is H,  $C_1$ - $C_6$  alkyl optionally substituted with OH; benzyl; NHC(O)-( $C_1$ - $C_6$  alkyl); -NHC(O)-phenyl wherein the phenyl is optionally substituted with 1 or 2 alkyl groups; - $CO_2$ -( $C_1$ - $C_6$  alkyl); - $CO_2$ -(benzyl); or -C(O)-( $C_1$ - $C_6$  alkyl).
  - 4. A compound according to claim 3 of the formula

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or a pharmaceutically acceptable salt thereof, wherein

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>
alkoxy, -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein the alkyl group is
optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), SO<sub>2</sub>-NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkyl),

[1,2,4]triazolidine-3,5-dione, -NHC(O)NH<sub>2</sub>, -NHC(O)NH(C<sub>1</sub>-C<sub>6</sub>
alkyl), -NHC(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub>
alkyl)C(O)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub>

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alkyl)C(0)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(0)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or (C<sub>1</sub>-C<sub>4</sub> alkyl)phenyl, -O-(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(S)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), (C<sub>1</sub>-C<sub>4</sub> alkyl)-O-phenyl, -C(0)-(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with NH<sub>2</sub>, N(C<sub>1</sub>-C<sub>6</sub> alkyl), or N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl); -O-C<sub>3</sub>-C<sub>6</sub> cycloalkyl, oxazole optionally substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(0)NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(0)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(0)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl))-N(C<sub>1</sub>-C<sub>6</sub> alkyl)pyridyl, -C(0)furanyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)-tetrahydrofuran, wherein the phenyl and pyridyl groups are unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, or

wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, azepanyl, pyridinyl, or pyrimidinyl ring, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, -C(O)NH<sub>2</sub>, or -C(O)NH-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl.

5. A compound according to claim 4 wherein  $R_{41}$  and  $R_{42}$  are both hydrogen.

- 6. A compound according to claim 4 wherein

  R<sub>35</sub> is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl).
- 7. A compound according to claim 3 wherein

  15 R<sub>35</sub> is phenyl, cyclohexyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, halo C<sub>1</sub>-C<sub>6</sub> alkyl, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);
- R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenylbenzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenylpyrimidinyl, -phenyl-isooxazolyl, -C(0)-pyridyl, -(C<sub>1</sub>-C<sub>4</sub>
  alkyl)-O-C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub>
  alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>,
  -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub>
  alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), CN, -(CH<sub>2</sub>)<sub>0-4</sub>-(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>1</sub>C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, C<sub>1</sub>-C<sub>8</sub>
  alkyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-NHC(O)-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>C(O)NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>0-4</sub>-C(O)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(CH<sub>2</sub>)<sub>0-4</sub>-C(O)N(C<sub>1</sub>-C<sub>6</sub>
  alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), tetrahydronapthyl, dihydronaphthyl,
  wherein each of the above is unsubstituted or substituted
  with 1, 2, 3, 4, or 5 groups that are independently

halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halo  $(C_1$ - $C_4$  alkyl), -0- $(C_1$ - $C_4$  alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO,  $C_1$ - $C_4$  thioalkoxy, -NHSO<sub>2</sub>- $(C_1$ - $C_4$  alkyl), -N( $C_1$ - $C_4$  alkyl)SO<sub>2</sub>- $(C_1$ - $C_4$  alkyl) wherein the alkyl groups are optionally substituted with 1, 2, or 3 halogens; OH, SO<sub>2</sub>R<sub>33</sub>, R<sub>33</sub>;

- $R_{41}$  is H, cyclohexyl, phenyl, or  $C_1-C_6$  alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or  $C_1-C_4$  thioalkoxy; and
- 10 R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.

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8. A compound according to claim 6 wherein
 R<sub>35</sub> is phenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -S-phenyl, benzodioxole, thienyl, C<sub>3</sub>-C<sub>6</sub> alkyl, furanyl, each of which is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, OH, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, halogen, CF<sub>3</sub>, OCF<sub>3</sub>, -Obenzyl, -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>5</sub>-C<sub>6</sub> cycloalkyl);

R40 is phenyl, -phenyl-pyridine, biphenyl, -phenyl-20 benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenylpyrimidinyl, -phenyl-isoxazolyl, -C(0)-pyridyl, - $(C_1-C_4)$  $alkyl) - O-C(O)NH-phenyl, -(C_1-C_4 alkyl) - O-C(O)N(C_1-C_6)$ alkyl)-phenyl,  $-(C_1-C_4 \text{ alkyl})$ -phenyl,  $-(C_1-C_4 \text{ alkyl})$ -SO<sub>2</sub>NH<sub>2</sub>,  $-(C_1-C_4 \text{ alkyl})-SO_2NH(C_1-C_6 \text{ alkyl}), -(C_1-C_4 \text{ alkyl})-SO_2N(C_1-C_6)$ alkyl)  $(C_1-C_6 \text{ alkyl})$ , CN,  $-(C_1-C_4 \text{ alkyl})-(C_3-C_6 \text{ cycloalkyl})$ , 25  $-(C_1-C_4 \text{ alkyl})-C(0)O-(C_1-C_4 \text{ alkyl}), -(C_1-C_4 \text{ alkyl})-R_{33}, C_1-C_8$ alkyl,  $-(C_1-C_4 \text{ alkyl})-NHC(0)-(C_1-C_4 \text{ alkyl})$ ,  $-C(0)NH_2$ , wherein each of the above rings is unsubstituted or substituted with 1, 2, or 3 groups that are independently 30 halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $CF_3$ , -0- $(C_1$ - $C_4$  alkyl)phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, -NHSO<sub>2</sub>-( $C_1$ - $C_4$  alkyl), -N( $C_1$ - $C_4$  $alky1)SO_2-(C_1-C_4 alky1)$  wherein the alkyl is optionally

substituted with 1, 2, or 3 halogens,

 $R_{41}$  is H, cyclohexyl, phenyl, or  $C_1-C_6$  alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or  $C_1-C_4$  thioalkoxy; and

R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN;

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5 R<sub>51</sub> at each occurrence is independently  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, -NHSO<sub>2</sub>-( $C_1$ - $C_4$  alkyl) wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO<sub>2</sub>-NH-( $C_1$ - $C_6$  alkyl)-NH<sub>2</sub>, -SO<sub>2</sub>-NH-( $C_1$ - $C_6$  alkyl)-NH( $C_1$ - $C_4$  alkyl), -SO<sub>2</sub>-NH-( $C_1$ - $C_6$  alkyl)-N( $C_1$ - $C_4$  alkyl),

10 [1,2,4]triazolidine-3,5-dione, -NHC(0)NH<sub>2</sub>, -NHC(0)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(0)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(0)NH<sub>2</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(0)NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -N(C<sub>1</sub>-C<sub>6</sub> alkyl)C(0)N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(0)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or 2-methylphenyl, -O-

optionally substituted with phenyl or 2-methylphenyl, -0-  $(C_1-C_4 \text{ alkyl})$ -phenyl, -NHC(S)NH<sub>2</sub>, -NHC(S)NH( $C_1-C_6 \text{ alkyl})$ , -NHC(S)N( $C_1-C_6 \text{ alkyl})$  ( $C_1-C_6 \text{ alkyl}$ ), ( $C_1-C_4 \text{ alkyl}$ )-0-phenyl, -C(0)-( $C_1-C_6 \text{ alkyl}$ ) wherein the alkyl group is optionally substituted with NH<sub>2</sub>, N( $C_1-C_6 \text{ alkyl}$ ), or N( $C_1-C_6 \text{ alkyl}$ ) ( $C_1-C_6 \text{ alkyl}$ )

 $C_6$  alkyl); -O- $C_3$ - $C_6$  cycloalkyl, oxazole optionally substituted with 1, or 2 groups that are independently  $C_1$ - $C_4$  alkyl or phenyl, hydroxy  $C_1$ - $C_4$  alkoxy, aminoalkoxy,  $NH(C_1$ - $C_6$ alkyl)-alkoxy,  $N(C_1$ - $C_6$ alkyl)( $C_1$ - $C_6$ alkyl)-alkoxy, wherein  $R_{31}$  and  $R_{32}$  at each occurrence are independently

selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkyl, -( $C_1$ - $C_6$  alkyl)-C(0)N( $C_1$ - $C_6$  alkyl)( $C_1$ - $C_6$  alkyl), -( $C_1$ - $C_6$  alkyl)-NH( $C_1$ - $C_6$  alkyl), -( $C_1$ - $C_6$  alkyl)) ( $C_1$ - $C_6$  alkyl), -( $C_1$ - $C_6$  alkyl)) pyridyl, -C(0) furanyl, ( $C_1$ - $C_6$  alkyl)-tetrahydrofuran, wherein

the phenyl group is unsubstituted or substituted with 1, 2, or 3 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,

wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, - C(O)NH<sub>2</sub>, or -C(O)NH-benzyl.

9. A compound according to claim 8 wherein

R<sub>35</sub> is phenyl; halophenyl, dihalophenyl; trihalophenyl;

tetrahalophenyl; pentahalophenyl; halo, benzyloxyphenyl;

halo, alkylphenyl; benzyloxyphenyl; cyclohexyl; (C<sub>1</sub>-C<sub>4</sub>

alkoxy)carbonylphenyl; (C<sub>1</sub>-C<sub>4</sub> alkoxy)phenyl; -S-phenyl, or

benzodioxole;

 $R_{41}$  is H, cyclohexyl, phenyl, or  $C_1-C_6$  alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or  $C_1-C_4$  thioalkoxy; and

 $R_{42}$  is hydrogen or -CH<sub>2</sub>CN.

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10. A compound according to claim 9 wherein  $R_{35}$  is 3,5-dihalophenyl;

Page 1 is phenyl, -phenyl-pyridine, biphenyl, -phenyl-benzothienyl, -phenyl-thienyl, -phenyl-furanyl, -phenyl-pyrimidinyl, -phenyl-isoxazolyl, -(C1-C4 alkyl)-O-C(O)NH-phenyl, -(C1-C4 alkyl)-O-C(O)N(C1-C6 alkyl)-phenyl, -(C1-C4 alkyl)-SO2NH2, CN, -(C1-C4 alkyl)-(C3-C6 cycloalkyl), -(C1-C4 alkyl)-C(O)O-(C1-C4 alkyl), -(C1-C4 alkyl)-R33, or C1-C8 alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C1-C4 alkyl, C1-C4 alkoxy, CF3, -O-(C1-C4 alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO2-(C1-C4 alkyl).

11. A compound according to claim 10 wherein R<sub>35</sub> is 3,5-difluorophenyl; 3,5-dichlorophenyl; or 3-chloro,5-fluorophenyl; and

- R<sub>40</sub> is phenyl which is unsubstituted or substituted with 1, 2, or 3 groups that are independently fluoro, chloro, bromo, iodo, methyl, ethyl, methoxy, ethoxy, CF<sub>3</sub>, or -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 groups that are independently halogen, or -NHSO<sub>2</sub>CH<sub>3</sub>.
- 10 A compound according to claim 11 wherein  $R_{51}$  at each occurrence is independently  $C_1-C_6$  alkyl,  $C_1-C_6$ alkoxy,  $-NHSO_2CH_3$ ,  $-SO_2-NH-(ethyl)$ - $NH(CH_3)$ , [1,2,4] triazolidine-3,5-dione, -NHC(0)NH<sub>2</sub>, -CF<sub>3</sub>, OH,  $-SO_2NR_{31}R_{32}$ ,  $-C(O)NR_{31}R_{32}$ , hydroxyoctyl, -CH(OH)-2-15 methylphenyl, -Obenzyl, or -NHC(S)NH(CH<sub>3</sub>); wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen; C1-C6 alkyl; hydroxy  $C_1-C_6$  alkyl;  $-(CH_2)C(O)N(CH_3)_2$ ; -CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>; benzyl which is optionally substituted 20 with 1 or 2 groups that are independently C1-C4 alkyl, C1-C4 alkoxy or halogen; phenethyl; -CH<sub>2</sub>CH<sub>2</sub>pyridyl; or -C(0) furanyl; or at each occurrence  $R_{31}$ ,  $R_{32}$  and the nitrogen to which they are attached independently form a pyrrolidinyl,

30 13. A compound according to claim 12 wherein  $R_{40}$  is 3-ethylphenyl or 3-methoxyphenyl; and  $R_{42}$  is hydrogen.

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14. A compound according to claim 12 wherein

piperazinyl, piperidinyl, or azepanyl, each of which

is optionally substituted with hydroxymethyl,

hydroxyethyl, methoxymethyl, or -C(O)NH2.

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R<sub>51</sub> at each occurrence is independently H, -SO<sub>2</sub>NH-propyl-OH, -
           SO_2NH-ethyl-OH, -SO_2NH-ethyl-OCH_3, -SO_2NH-CH(CH_3)_2-CH_2OH, -
           SO_2NH-(CH_2CH(OH)CH_3), -SO_2NH-ethyl-NH(CH_3), -
           SO_2NH(CH_2CH_2OH)_2, -SO_2NHCH(CH_3)CH_2OH, -SO_2N(CH_3)_2, -
 5
           SO_2NH(CH_2CH(OH)CH_3), -SO_2-pyrrolidine, -SO_2-(2,6-
          dimethylpiperidine), -SO<sub>2</sub>-(2-propylpiperidine), -SO<sub>2</sub>-
           (hydroxypropyl), -C(0)-(2-methoxymethylpyrrolidine), -
          C(0)-(2-methylpyrrolidine), -C(0)-(2,6-
          dimethylpyrrolidine),-C(0)-(2-hydroxymethylpyrrolidine),
10
           -C(O)N(methyl)(ethyl), -C(O)N(methyl)(propyl),
          -C(0)N(methyl)(butyl), -C(0)N(propyl)(butyl),
          -C(0)N(allyl)(cyclopentyl), -C(0)N(allyl)(cyclohexyl),
          -C(0)N(methyl) (methyl), -C(0)N(ethyl) (ethyl),
          -C(0)N(butyl)(butyl), -C(0)N(isopropyl)(isopropyl),
15
          -C(0)N(propyl)(propyl), -C(0)N(methyl)(cyclohexyl),
          -C(0)N(ethyl)(cyclohexyl), -C(0)NH(cyclobutyl),
          -C(0)NH(cyclopentyl), -C(0)N(CH<sub>3</sub>)(cyclopentyl), -C(0)NH(2-
          methylcyclohexyl), -C(0)NH(pentyl),
          -C(0)N(pentyl) (pentyl), -C(0)NH(isopentyl), -
20
          C(0)NH(ethoxyethyl), -C(0)N(CH<sub>3</sub>)(methoxyethyl),
          -C(0)N(propyl) (methoxyethyl),
          -C(0)N(methoxyethyl)(methoxyethyl),
        -C(0)N(ethoxyethyl)(ethoxyethyl),
          -C(0)N(ethyl)(methoxyethyl), -C(0)N(propyl)(hydroxyethyl),
25
          -C(0)N(hydroxyethyl)(ethyl), ethynyl, methyl, bromo,
          -N(CH_3)SO_2(CH_3), -N(CH_3)SO_2-thienyl, -
          N(hydroxypropy1)SO_2CH_3, -CH_2)-SO_2-(CH_3), or -C(O)-C(O)
          CH (CH<sub>3</sub>) CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.
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- 15. A compound according to claim 14 wherein there are two  $R_{51}$  groups.
  - 16. A compound according to claim 15 wherein the  $R_{51}$  groups are at the 3 and 5 positions of the phenyl group.

17. A compound according to claim 11 wherein R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -C(0)NR<sub>31</sub>R<sub>32</sub>, -C(0)CH<sub>2</sub>NH<sub>2</sub>, cyclopentyloxy, -NHC(0)NH(ethyl), oxazole optionally substituted with 1 or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl, hydroxyethoxy, diethylaminoethoxy, wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -CH<sub>2</sub>-tetrahydrofuran.

- 18. A compound according to claim 9 wherein  $R_{35}$  is cyclohexyl.
- 15 19. A compound according to claim 15 wherein R<sub>40</sub> is phenyl, or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo (C<sub>1</sub>-C<sub>4</sub> alkyl); and
- 20  $R_{42}$  and  $R_{41}$  are both hydrogen.

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- 20. A compound according to claim 16 wherein

  R<sub>40</sub> is phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3
  ethoxyphenyl, 4-ethoxyphenyl, 3-trifluoromethylphenyl, 4
  trifluoromethylphenyl, 2-methylphenyl, 3-methylphenyl, 2
  ethylphenyl, 3-ethylphenyl, or C<sub>3</sub>-C<sub>6</sub> alkyl; and

  R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>

  alkoxy, or halogen,
- wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently

  selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>

  alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and -(C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl

  wherein the phenyl group is unsubstituted or

  substituted with 1, 2, or 3 groups that are

  independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,

wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, piperidinyl, or azepanyl, each of which is optionally fused to a benzene, pyridine or pyrimidine ring and each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(0)NH<sub>2</sub>, or -C(0)NH-benzyl.

- 21. A compound according to claim 9 wherein R<sub>35</sub> is 3-halo, 5-benzyloxyphenyl; 3-benzyloxyphenyl; or 4-benzyloxyphenyl;
- R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.
- 22. A compound according to claim 21 wherein

  R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O
  C(O)NH-phenyl, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-O-C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl,
  -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>NH<sub>2</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkyl)-(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), 
  (C<sub>1</sub>-C<sub>4</sub> alkyl)-C(O)O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-R<sub>33</sub>, or C<sub>1</sub>
  C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens,
  -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl).
- 23. A compound according to claim 22 wherein

  30 R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is
  unsubstituted or substituted with 1, 2, or 3 groups that
  are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>,

  -Obenzyl wherein the phenyl is optionally substituted with

  1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and

 $R_{41}$  is hydrogen or  $C_1$ - $C_6$  alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or  $C_1$ - $C_4$  thioalkoxy;  $R_{42}$  is hydrogen; and

R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> 5 alkoxy,  $-NHSO_2-(C_1-C_4 \text{ alkyl})$  wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO2-NH- $(C_1-C_6 \text{ alkyl})-NH_2$ ,  $-SO_2-NH-(C_1-C_6 \text{ alkyl})-NH(C_1-C_4 \text{ alkyl})$ , - $SO_2$ -NH-( $C_1$ - $C_6$  alkyl)-N( $C_1$ - $C_4$  alkyl)( $C_1$ - $C_4$  alkyl),  $-NHC(O)NH_2$ ,  $-NHC(O)NH(C_1-C_6 alkyl)$ ,  $-NHC(O)N(C_1-C_6)$ 10 alkyl)  $(C_1-C_6 \text{ alkyl})$ ,  $-N(C_1-C_6 \text{ alkyl})C(0)NH_2$ ,  $-N(C_1-C_6 \text{ alkyl})C(0)NH_2$  $alkyl)C(O)NH(C_1-C_6 \ alkyl), -N(C_1-C_6 \ alkyl)C(O)N(C_1-C_6$ alkyl)( $C_1-C_6$  alkyl), halogen,  $-CF_3$ , OH,  $-SO_2NR_{31}R_{32}$ , - $C(0)NR_{31}R_{32}$ ,  $-NR_{31}R_{32}$ , hydroxy  $C_1-C_{10}$  alkyl, -Obenzyl, - $NHC(S)NH_2$ ,  $-NHC(S)NH(C_1-C_6 alkyl)$ ,  $-NHC(S)N(C_1-C_6 alkyl)(C_1-C_6 alkyl)$ 15  $C_6$  alkyl),  $(C_1-C_4$  alkyl)-0-phenyl,  $-C(0)-(C_1-C_6$  alkyl), -0cyclopentyl, -0-cyclohexyl, hydroxy  $C_1$ - $C_4$  alkoxy, aminoalkoxy,  $NH(C_1-C_6alkyl)-alkoxy$ ,  $N(C_1-C_6alkyl)(C_1-C_6alkyl)$ 

wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently

selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>

alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub>

alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), and

benzyl wherein the phenyl group is unsubstituted or

substituted with 1, or 2 groups that are

independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen,

 $C_6$ alkyl)-alkoxy,

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wherein at each occurrence  $R_{31}$ ,  $R_{32}$  and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of which is optionally substituted with hydroxy, hydroxy  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy  $C_1$ - $C_6$  alkyl, -C(0)NH<sub>2</sub>, or -C(0)NH-benzyl.

24. A compound according to claim 23 wherein

 $R_{40}$  is phenyl or  $C_1$ - $C_8$  alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or  $CF_3$ ; and

- 5 R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,
- wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and benzyl wherein the phenyl group is unsubstituted or substituted with 1 or 2 groups that are independently methoxy, ethoxy, or halogen, or
  - wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl ring each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, or-C(0)NH<sub>2</sub>.
- 25. A compound according to claim 24 wherein R<sub>35</sub> is 3-fluoro, 5-benzyloxyphenyl or 3-chloro, 5-benzyloxyphenyl.

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- 26. A compound according to claim 9 wherein

  R<sub>35</sub> is -S-phenyl, benzo[1,3]dioxole, furanyl, or thienyl;

  R<sub>41</sub> is H, cyclohexyl, phenyl, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally

  substituted with 1 or 2 groups that are phenyl, hydroxy, or C<sub>1</sub>-C<sub>4</sub> thioalkoxy; and

  R<sub>42</sub> is hydrogen or -CH<sub>2</sub>CN.
  - 27. A compound according to claim 26 wherein

R<sub>40</sub> is phenyl, -phenyl-pyridine, biphenyl, -phenyl-pyrimidinyl,  $-(C_1-C_4 \text{ alkyl})-O-C(0)NH-\text{phenyl}, -(C_1-C_4 \text{ alkyl})-O-C(0)N(C_1-C_6 \text{ alkyl})-\text{phenyl}, -(C_1-C_4 \text{ alkyl})-SO_2NH_2, -(C_1-C_4 \text{ alkyl})-(C_3-C_6 \text{ cycloalkyl}), -(C_1-C_4 \text{ alkyl})-C(0)O-(C_1-C_4 \text{ alkyl}), -(C_1-C_4 \text{ alkyl})-R_{33}, \text{ or } C_1-C_8 \text{ alkyl}, \text{ wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, <math>C_1-C_4 \text{ alkyl}, C_1-C_4 \text{ alkoxy}, CF_3$ , -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHSO<sub>2</sub>CF<sub>3</sub>.

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28. A compound according to claim 27 wherein  $R_{51}$  at each occurrence is independently selected from the group consisting of

 $C_1-C_4 \text{ alkyl, } -C(0)N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl}), -C(0)NH_2,$   $-C(0)N(C_2-C_6 \text{ alkenyl})(C_3-C_8 \text{ cycloalkyl}), -C(0)NH(C_3-C_8 \text{ cycloalkyl}), -C(0)NH(C_1-C_6 \text{ alkyl}), C(0)-(pyrrolidine) optionally substituted with 1 or two groups that are independently alkoxyalkyl or hydroxy, halogen, -C(0)N(C_1-C_6 hydroxyalkyl)(C_1-C_6 alkyl), -C(0)NH(alkoxyalkyl), -C(0)N(C_1-C_6 alkyl), -C(0)N(C_1-C_6 alkyl)$ 

-C(O)N(alkoxyalkyl) (alkoxyalkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> alkyl) (alkoxyalkyl), -C(O)N(C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl) (alkyl), -NHSO<sub>2</sub>CF<sub>3</sub>, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-SO<sub>2</sub>-thienyl, -N(C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl)SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub> alkyl), -NHC(O)C<sub>1</sub>-C<sub>4</sub> alkyl, oxazolyl optionally substituted with 1 or 2 methyl groups, thiazolyl optionally substituted with 1 or 2 methyl groups, pyrazolyl optionally substituted with 1 or 2 methyl groups, imidazolyl optionally substituted with 1 or 2 methyl groups, imidazolyl optionally

substituted with 1 or 2 methyl groups, isoxazolyl optionally substituted with 1 or 2 methyl groups, pyrimidinyl optionally substituted with 1 or 2 methyl or halogen groups, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>-imidazolyl wherein the imidazole ring is optionally substituted

with 1 or 2 methyl groups,  $-N(C_1-C_6 \text{ alkyl})SO_2(C_1-C_6)$ 

alkyl), -SO<sub>2</sub>NH-C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, -SO<sub>2</sub>NH-C<sub>1</sub>-C<sub>6</sub> alkyl-NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>-piperazinyl optionally substituted with 1 or 2 methyl groups, -SO<sub>2</sub>-pyrrolidine optionally substituted with 1 or 2 methyl groups, -SO<sub>2</sub>-piperidine optionally substituted with 1 or 2 C<sub>1</sub>-C<sub>4</sub> alkyl groups, -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl)(C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl), -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl), -(C<sub>1</sub>-C<sub>4</sub> alkyl)-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl), or -C(O)-(C<sub>1</sub>-C<sub>1</sub>0 alkyl).

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29. A compound according to claim 28 wherein

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R<sub>51</sub> at each occurrence is independently selected from the group
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            consisting of -SO<sub>2</sub>NH-propyl-OH, -SO<sub>2</sub>NH-ethyl-OH, -SO<sub>2</sub>NH-
            ethyl-OCH<sub>3</sub>, -SO_2NH-CH(CH_3)_2-CH_2OH, -SO_2NH-(CH_2CH(OH)CH_3), -
            SO<sub>2</sub>NH-ethyl-NH(CH<sub>3</sub>), -SO<sub>2</sub>NH(-CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, -SO<sub>2</sub>NHCH(CH<sub>3</sub>)CH<sub>2</sub>OH,
            -SO<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, -SO<sub>2</sub>NH(CH<sub>2</sub>CH(OH)CH<sub>3</sub>), -SO<sub>2</sub>-pyrrolidine, -SO<sub>2</sub>-
            (2,6-dimethylpiperidine), -SO<sub>2</sub>-(2-propylpiperidine), -SO<sub>2</sub>-
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            (hydroxypropyl), -C(0)-(2-methoxymethylpyrrolidine), -
            C(0)-(2-methylpyrrolidine), -C(0)-(2,6-
            dimethylpyrrolidine),-C(0)-(2-hydroxymethylpyrrolidine),
            -C(O)N(methyl)(ethyl), -C(O)N(methyl)(propyl),
            -C(O)N(methyl)(butyl), -C(O)N(propyl)(butyl),
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            -C(O)N(allyl)(cyclopentyl), -C(O)N(allyl)(cyclohexyl),
            -C(O)N(methyl) (methyl), -C(O)N(ethyl) (ethyl),
            -C(0)N(butyl)(butyl), -C(0)N(isopropyl)(isopropyl),
            -C(O)N(propyl)(propyl), -C(O)N(methyl)(cyclohexyl),
            -C(O)N(ethyl)(cyclohexyl), -C(O)NH(cyclobutyl),
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            -C(0)NH(cyclopentyl), -C(0)N(CH<sub>3</sub>)(cyclopentyl), -C(0)NH(2-
            methylcyclohexyl), -C(0)NH(pentyl),
            -C(O)N(pentyl)(pentyl), -C(O)NH(isopentyl), -
            C(0)NH(ethoxyethyl), -C(0)N(CH<sub>3</sub>)(methoxyethyl),
            -C(O)N(propyl) (methoxyethyl),
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-C(O)N(methoxyethyl)(methoxyethyl),
-C(O)N(ethoxyethyl)(ethoxyethyl),
-C(O)N(ethyl)(methoxyethyl), -C(O)N(propyl)(hydroxyethyl),
-C(O)N(hydroxyethyl)(ethyl), ethynyl, methyl, bromo,
-N(CH<sub>3</sub>)SO<sub>2</sub>(CH<sub>3</sub>), -N(CH<sub>3</sub>)SO<sub>2</sub>-thienyl, -
N(hydroxypropyl)SO<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)-SO<sub>2</sub>-(CH<sub>3</sub>), or -C(O)-
CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.
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- 30. A compound according to claim 27 wherein
- 10 R<sub>40</sub> is phenyl or C<sub>1</sub>-C<sub>8</sub> alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, CF<sub>3</sub>, -Obenzyl wherein the phenyl is optionally substituted with 1 or 2 halogens, -CHO, or -NHSO<sub>2</sub>-(C<sub>1</sub>-C<sub>4</sub> alkyl); and
- 15  $R_{41}$  is hydrogen or  $C_1$ - $C_6$  alkyl optionally substituted with 1 or 2 groups that are phenyl, hydroxy, or  $C_1$ - $C_4$  thioalkoxy; and;

R<sub>42</sub> is hydrogen; and

 $R_{51}$  at each occurrence is independently  $C_1-C_6$  alkyl,  $C_1-C_6$ 20 alkoxy,  $-NHSO_2-(C_1-C_4 \text{ alkyl})$  wherein the alkyl group is optionally substituted with 1, 2, or 3 halogens, -SO2-NH- $(C_1-C_6 \text{ alkyl})-NH_2$ ,  $-SO_2-NH-(C_1-C_6 \text{ alkyl})-NH(C_1-C_4 \text{ alkyl})$ , - $SO_2$ -NH-( $C_1$ - $C_6$  alkyl)-N( $C_1$ - $C_4$  alkyl)( $C_1$ - $C_4$  alkyl),  $-NHC(0)NH_2$ ,  $-NHC(0)NH(C_1-C_6 alkyl)$ ,  $-NHC(0)N(C_1-C_6)$ 25 alkyl)  $(C_1-C_6 \text{ alkyl})$ ,  $-N(C_1-C_6 \text{ alkyl})C(0)NH_2$ ,  $-N(C_1-C_6 \text{ alkyl})C(0)NH_2$  $alkyl)C(O)NH(C_1-C_6 \ alkyl), -N(C_1-C_6 \ alkyl)C(O)N(C_1-C_6$ alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), halogen, -CF<sub>3</sub>, OH,  $-SO_2NR_{31}R_{32}$  $-C(0)NR_{31}R_{32}$ ,  $-NR_{31}R_{32}$ , hydroxy  $C_1-C_{10}$  alkyl, -Obenzyl, - $NHC(S)NH_2$ ,  $-NHC(S)NH(C_1-C_6 alkyl)$ ,  $-NHC(S)N(C_1-C_6 alkyl)(C_1-C_6 alkyl)$ 30  $C_6$  alkyl),  $(C_1-C_4$  alkyl)-0-phenyl,  $-C(0)-(C_1-C_6$  alkyl), -0cyclopentyl, -0-cyclohexyl, hydroxy  $C_1$ - $C_4$  alkoxy, aminoalkoxy,  $NH(C_1-C_6 \text{ alkyl})-alkoxy$ ,  $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$ alkyl)-alkoxy,

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wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)-NH(C<sub>1</sub>-C<sub>6</sub> alkyl), -(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(C<sub>1</sub>-C<sub>6</sub> alkyl)(C<sub>1</sub>-C<sub>6</sub> alkyl), and benzyl wherein the phenyl group is unsubstituted or substituted with 1, or 2 groups that are independently C<sub>1</sub>-C<sub>4</sub> alkoxy, or halogen, wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to

wherein at each occurrence R<sub>31</sub>, R<sub>32</sub> and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl, each of which is optionally substituted with hydroxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, -C(0)NH<sub>2</sub>, or -C(0)NH-benzyl.

- 31. A compound according to claim 30 wherein  $R_{40}$  is phenyl or  $C_1$ - $C_8$  alkyl, wherein each of the above is unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, or  $CF_3$ ; and
- 20 R<sub>51</sub> at each occurrence is independently C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, -NHSO<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>CF<sub>3</sub>, halogen, -CF<sub>3</sub>, OH, -SO<sub>2</sub>NR<sub>31</sub>R<sub>32</sub>, -C(O)NR<sub>31</sub>R<sub>32</sub>, -NR<sub>31</sub>R<sub>32</sub>, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy, aminoalkoxy, NH(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy, N(C<sub>1</sub>-C<sub>6</sub>alkyl)(C<sub>1</sub>-C<sub>6</sub>alkyl)-alkoxy,
- wherein R<sub>31</sub> and R<sub>32</sub> at each occurrence are independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, and benzyl wherein the phenyl group is unsubstituted or substituted with 1 or 2 groups that are independently methoxy, ethoxy, or halogen, or
  - wherein at each occurrence  $R_{31}$ ,  $R_{32}$  and the nitrogen to which they are attached independently form a pyrrolidinyl, piperazinyl, or piperidinyl ring each of which is optionally substituted with hydroxy,

hydroxy  $C_1-C_6$  alkyl,  $C_1-C_4$  alkoxy  $C_1-C_6$  alkyl, or-C(0) NH<sub>2</sub>.

## 32. A compound of the formula:

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or a pharmaceutically acceptable salt thereof, wherein R<sub>30</sub> is selected from the group consisting of phenyl, pyrazolopyrimidinyl, oxa-aza-benzoazulenyl, isoxazolyl, triazolopyridinyl, pyrrolidinonyl, tetrahydrothia-aza-10 fluorenyl, pyridyl, piperidinyl, dihydrocyclopentaquinolinyl, furyl, naphthothienyl, phthalazinonyl, thiadiazolyl, thienopyrimidinonyl, oxadiaza-cyclopentanaphthalenyl, dihydrobenzodioxepinyl, chromanonyl, chromenonyl, oxazolidinyl, purinyl, oxaxolyl, 15 thiazolyl, pyridazinonyl, thiazolyl, pyranyl, dihydropyranopyridinyl, diazepanyl, cyclopropyl, dihydronaphthoisoxazolyl, benzoindazole, dihydrocyclopentachromenonyl, imidazopyrazolyl, tetrahydrocyclopentachromenonyl, dihydroquinolinonyl, 20 pyridyl, isochromanyl, quinazolinonyl, pyrazolopyridinyl, dihydrobenzothiophene dioxide, dihydrofurobenzoisoxazolyl, dihydropyrimidine dionyl, thienopyrazolyl, oxazolyl, tetrahydrocyclopentapyrazolyl, dihydronaphthalenonyl, dihydrobenzofuranonyl, dihydrocyclopentathienyl, 25 tetrahydrocyclopentapyrazolyl, tetrahydropyrazoloazepinyl, indazolyl, tetrahydrocycloheptaisoxazolyl, tetrahydroindolonyl, pyrrolidinyl, thienopyridinyl, dioxodihydrobenzoisothiazolonyl, triazolopyrimidinyl, thienyl, dihydrothienopyrimidinonyl, and benzooxadiazolyl, 30 wherein each of the above is unsubstituted or substituted with 1, 2, 3, 4, or 5 groups that are independently selected from the group consisting of

 $C_1-C_{10}$  alkyl optionally substituted with phenyl, hydroxy, hydroxy C<sub>1</sub>-C<sub>10</sub> alkyl optionally substituted with phenyl or  $(C_1-C_4 \text{ alkyl})$  phenyl,  $C_1-C_6 \text{ alkoxy optionally}$ substituted with 1 or 2 hydroxy groups, -C(0)NR<sub>31</sub>R<sub>32</sub>, 5  $-NR_{31}-SO_2-(C_1-C_6 \text{ alkyl})$  wherein the alkyl group is optionally substituted with 1, 2, or 3 R<sub>33</sub> groups, -SO<sub>2</sub>-NH(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein the alkyl group is optionally substituted with 1 or 2 R<sub>33</sub> groups, -SO<sub>2</sub>- $N(C_1-C_6 \text{ alkyl})(C_1-C_6 \text{ alkyl})$  wherein each alkyl group 10 is optionally substituted with 1 or 2 R<sub>33</sub> groups, - $SO_2$ -NH( $C_1$ - $C_6$  alkyl)-phenyl wherein the phenyl is optionally substituted with 1 or 2 groups that are independently  $C_1-C_4$  alkoxy or halogen,  $-0-(C_1-C_6)$ alkyl)-phenyl,  $-(C_1-C_6 \text{ alkyl})-O-\text{phenyl}$ ,  $-(C_1-C_6 \text{ alkyl})$ 15 alkyl)-O-(C<sub>1</sub>-C<sub>6</sub> alkyl)-phenyl, triazolidine-3,5dione, halogen,  $-NHC(0)NH_2$ ,  $-N(C_1-C_6 alkyl)C(0)NH_2$ ,  $-N(C_1-C_6 \text{ alkyl})C(O)NH(C_1-C_6 \text{ alkyl}), -N(C_1-C_6)$  $alkyl)C(0)N(C_1-C_6 \ alkyl)(C_1-C_6 \ alkyl), -(C_1-C_6 \ alkyl)$ thienyl,  $-(C_1-C_6 \text{ alkyl})$  furanyl,  $-S-(C_1-C_6 \text{ alkyl})$ phenyl,  $-SO_2NR_{31}R_{32}$ , -C(O)  $-NR_{31}R_{32}$ ,  $-NR_{31}R_{32}$ , dithiane, 20  $-NHC(S)NH_2$ ,  $-NHC(S)NH(C_1-C_6 alkyl)$ ,  $-NHC(S)N(C_1-C_6)$ alkyl)  $(C_1-C_6 \text{ alkyl})$ ,  $-CO_2(C_1-C_6 \text{ alkyl})$ , tetrahydropyran, phenyl optionally substituted with 1 or 2 groups that are independently F, Cl or Br, 25 pyridine, -C<sub>2</sub>-C<sub>4</sub> alkynyl-phenyl, -O-C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  $-O-(C_1-C_6 \text{ alkyl})-R_{33}$ , benzo[1,2,5]oxadiazole, -C(O)- $(C_1-C_6 \text{ alkyl})$  wherein the alkyl group is optionally substituted with  $NH_2$ ,  $N(C_1-C_6 \text{ alkyl})$ , or  $N(C_1-C_6)$ alkyl)  $(C_1-C_6 \text{ alkyl})$ ; -C(O)NH-phenyl,  $-C(O)N(C_1-C_6)$ 30 alkyl)-phenyl, 4,4-Dimethyl-4,5-dihydro-oxazole, - $(C_1-C_6 \text{ alkyl})-S-pyridine, -(C_1-C_6 \text{ alkyl})-SO_2-pyridine,$  $-(C_1-C_6 \text{ thioalkoxy}) - \text{pyridine},$ 

wherein  $R_{31}$  and  $R_{32}$  at each occurrence are independently selected from the group consisting of hydrogen,  $C_1$ - $C_6$